

THE USE OF PENICILLIN IN THE
NOSE AND THROAT

being a

Thesis for the degree of M.D.
of the University of Edinburgh

by

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INTRODUCTION.

THE SUBJECT:

This thesis is intended as a short treatise on the work I have done recently in an Ear, Nose and Throat Hospital regarding the local and systemic application of Penicillin, and the possibilities of its use in the treatment of common infective conditions of the Nose and Throat.

THE OBJECT:

The objects of the investigation were to discover what conditions met with in our sphere were amenable to Penicillin treatment, and then by comparison with the routine methods in use, to decide whether such treatment represented any therapeutic advance.

THE SOURCE:

The ensuing material is the result of observations based on Bacteriological and Clinical Studies with the addition of introductory discussion of the available literature on each subject.

THE TIME AND PLACE

The Clinical work was undertaken while I was in turn Resident and Clinical Assistant to Dr I. Simson

Hall in the Ear, Nose and Throat Department of the Royal Infirmary of Edinburgh and to whom I am deeply indebted for patient counsel and encouragement. The clinical material was derived from both in-patients and out-patients under his care.

The Bacteriological studies were carried out in the Royal Infirmary Laboratories by courtesy of Dr W. R. Logan, to whom I am also very grateful.

The Bibliography was compiled with the assistance of the Librarians to the Central Medical Library, University of Edinburgh.

THE AGENT.

Penicillin, a very recent addition to our pharmacopoeia, has proved to be one of the most valuable and powerful antibacterial agents yet discovered. It has proved, however, like all valuable drugs, to have a limited though extremely wide range of antibacterial activity and field of action.

One such limitation is its destruction by the gastric acids (Florey, 1943) which prevented administration by the easy oral route (a difficulty since overcome) but not its oral or nasal administration for local activity in the upper respiratory tract, infections of which are some of the commonest conditions

met with in Ear, Nose and Throat Clinics.

In this field, its use has been suggested in the form of a solution, either applied as a spray or incorporated in a lozenge, or of a dry powder for insufflation.

Other workers (MacGregor and Long, 1944) showed that a spray gave too transient an action and too low a concentration and that continuous diffusion was required, and suggested the use of a pastille, which in their case consisted of gelatin and 0.1% nipagin containing 500 units of Penicillin, to be retained in the buccal sulcus for as long as possible.

The use of Penicillin powder as a nasal snuff was suggested by Delafield, Straker and Topley (1941), and later Fleming (1945) reported the use of dried plasma as a suitable diluent for such local application.

The following work concerns further investigations on the local use of Penicillin as lozenge and snuff, and its local and systemic use in infections of the paranasal sinuses.

The work is divided into three sections dealing with the mouth and throat, the nose, and the paranasal sinuses respectively.

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SECTION 1.

THE USE OF PENICILLIN LOZENGES
IN THE MOUTH AND THROAT.

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CHAPTER I.

EXPERIMENTAL METHODS.

CHAPTER I.EXPERIMENTAL METHODS.(1) The Penicillin Lozenge.

As mentioned in the Introduction, other workers had suggested gelatin and 0.1 nipagin as the base to use. Trial in this hospital determined that a gelatin base was not altogether satisfactory owing to the lozenge's melting and dissolving rapidly in the mouth, producing an immediate but transient concentration and bitter taste, with discomfort from the very sticky salivary mixture. Moreover it was necessary to ensure a constant effective concentration for an adequate period of time, so that the means of a more even distribution had to be found.

The lozenge finally chosen was one of plain agar 4-10%, the higher percentage the better for its duration in the mouth, containing about 500-1000 units, and of suitable size to be retained in the buccal sulcus, approximately $\frac{1}{4}$ " square and $\frac{1}{8}$ " in thickness. These were prepared by melting the required amount of agar, and adding 2 cc. (120,000 units) of Penicillin solution when sufficiently cool and just before pouring into a medium sized Petri-dish. When set, the

contents of the dish were cut into lozenges by cross-hatching with a sterile scalpel and these were then turned out into small sterile bottles of 20 lozenges.

Early trial with such lozenges held in the buccal sulcus for as long as possible resulted in a measured salivary content of about 1 unit per cc. saliva two hours after inserting the lozenge.

As the investigations and clinical trials proceeded, modifications were suggested by patients and staff alike. One of these was the flavouring of the lozenges to mask the slight but bitter taste of the impure Penicillin. Oils of peppermint and raspberry were tried, and from the patients' point of view proved very palatable. The addition of oil, however, softened the lozenge considerably, and what with the constant desire to suck the pleasant flavour, it rapidly disintegrated. Moreover, in view of possible side-actions or inhibition of the Penicillin, it was thought undesirable to introduce any non-essential substance, and so the use of the plain agar lozenge continued.

(2) Administration of the Lozenge.

In the wards the lozenges were given by placing one by means of sterile forceps in a teaspoon from which the patient licked it into the buccal sulcus or

under the tongue, wherever he was least likely to suck or chew it, being given instructions to retain it intact for as long as possible.

One such lozenge was given every two hours during the day and every four hours by night - 10 lozenges per 24 hours.

(3) Clinical Methods.

These varied with the different conditions under study, and are best considered under their respective headings.

(4) Bacteriological Methods.

In every case, the bacterial flora was recorded by means of swabs taken from the throat, mouth or nose as the case might be. All were taken under direct vision and with every precaution to avoid contamination, using a head mirror and reflected light, with a tongue depressor (Lack's spatula) or nasal speculum (Thudicum's). The swabs from cases of Vincent's infection were smeared on microscope slides to make direct films, stained methyl violet; all other swabs were as soon as possible plated out by flaming the mouth of the test-tube, rubbing the swab a few times over a small segment of Blood Agar Plate so as to form "the well", from which the organisms were spread by cross-hatching with a sterile wire

loop. In the case of swabs taken from patients who had already received any Penicillin, special Penicillinase plates were used to eliminate the possibility of any active Penicillin being carried over and inhibiting growth on the plate. These were prepared by allowing one cubic centimetre of Penicillinase to spread over an ordinary Blood Agar plate which was then dried for an hour in the incubator and inoculated in the manner described above.

The plates were incubated for at least 24 hours.

The resulting colonies were then identified by naked eye or low power magnification, this being confirmed by microscopic examination of a film stained by Gram's method (and by Neisser's method in the case of diphtheroids). Colony counts were then recorded, enumerating only those in the spread area outside the well, except where the organisms were so few as to be absent from the spread area but occurring in small numbers in the well, when their numbers therein were recorded in parenthesis. In the case of smears from Vincent's infection, counts were made of the average numbers of spirochaetes and bacilli per microscopic field.

Identification was carried a stage further by sub-culture where necessary: non-haemolytic streptococci

were plated on McConkey's medium to differentiate the viridans and faecalis strains; staphylococci were subcultured on serum-agar slopes for later coagulase test of virulence; diphtheroid bacilli were similarly subcultured for inoculation of glucose, saccharose and dextrin, and the Gram-negative diplococci for inoculation of glucose, maltose, lactose and saccharose; coliform bacilli were plated on McConkey's medium for inoculation of glucose, lactose and mannitol.

When there was any doubt as to an organism, generally regarded as being sensitive to Penicillin, resisting its bactericidal action, Penicillin sensitivity tests were performed. In this a gutter was cut across a Blood Agar plate at one side, and a loopful of the organisms in question spread out at right-angles to the gutter. Two or three such organisms could be tested simultaneously, and on each plate was also spread a standard strain of susceptible staph. aureus as a control. The gutter was filled with two units per cc. Penicillin and the plate incubated for 24 hours, when sensitivity to Penicillin was shown by a zone of inhibition extending to about 1 cm. from the gutter; resistance to one unit per cc. Penicillin permitted growth to the edge of the gutter.

(5) Scheme of Investigations.

As there was little literature on the subject and as a new form of lozenge was being used, I decided it was better to start from 'scratch', assuming nothing and requiring to prove any antibacterial effect they had.

The first essential then was to devise a series of experiments covering estimations of their activity, its degree and duration, their penetration, and their effectiveness in practical ward use.

This done, I chose for clinical trials three conditions met with in our hospital practice, namely tonsillectomy and its sequelae, acute streptococcal infections, and Vincent's infection.

Detailed accounts of these experiments and clinical investigations follow in Chapters II and III.

CHAPTER II.

CLINICAL EXPERIMENTS.

CHAPTER II.

THE EXPERIMENTS.

PROGRAMME of EXPERIMENTS.

Experiment I.

Object: Have Penicillin Lozenges any effect on the bacterial flora of the Fauces, and if so how many are required?

Experiment II.

Object: What is the time, after administration, of optimum effect of one Penicillin lozenge, and what is the duration of that effect?

Experiment III.

Object: What is the minimum number of lozenges, given at intervals of two hours, required to produce sterility of the fauces, and for how long does that sterile field persist?

Experiment IV.

Object: Having proposed a scheme of administration for attaining sterility of the fauces, is the method effective in practice?

Experiment V.

Object: Does the Penicillin administered as in Experiment IV sterilize the depths of the Tonsillar Crypts as well as the Faucial Surface?

Experiment VI.

Object: Having proposed a scheme of administration for attaining post-operative sterility of Fauces, is the method effective in practice?

EXPERIMENT I.

Object: Have Penicillin Lozenges any effect on the bacterial flora of the fauces, and if so, how many are required?

Subjects: Ambulant post-mastoidectomy cases who had a history of previous attacks of 'sore throat', but who had then no obvious active infection.

Method: Eight such patients were chosen and throat swabs taken from the surface of both tonsils. They were then divided into four groups of two patients, each group to receive one, two, three or four lozenges at 2-hourly intervals, a final throat swab being taken at two hours after the last lozenge.

Results: See Table I.

TABLE I.

| Organisms - number of colonies before and after Penicillin Lozenges. | | | | | | | | | | | |
|--|---------|------------------|----------------|------------------|------------|-----------------|-------|-------------------|------------|-----------------|-----------|
| Number of Lozenges | Case | Strep. pyogenes | | Strep. viridans | | Strep. faecalis | | Diplo catarrhalis | | Staph. albus | |
| | | Before Lozenges | After Lozenges | Before | After | Before | After | Before | After | Before | After |
| 1 { | 5 7 | 100 120 | nil nil | 800 | 400 | 400 | 500 | | | 215 13 | 185 17 |
| 2 { | 4 6 | 400 | nil | 1200 400 | nil 400 | 100 | 80 | 35 20 | nil nil | 100 12 | 46 60 |
| 3 { | 9 10 | 2 | nil | 400 600 | 400 nil | 400 | 400 | 125 500 | nil nil | | |
| 4 { | 8 11 | 16 | nil | 400 800 | nil nil | | | 200 200 | nil 5 | | |
| Elimination in | | 5 out of 5 cases | | 4 out of 7 cases | | None of 3 cases | | 5 out of 6 cases | | None of 4 cases | |

From the table it can be seen that:

- (a) In the 5 cases in which Strep. pyogenes occurred, that organism was eliminated no matter the number of lozenges.
- (b) Of the 6 cases in which Diplo. catarrhalis occurred, in 5 cases that organism was eliminated and in the other greatly reduced.
- (c) Of the 7 cases in which Strep. viridans occurred, that organism was eliminated in 4 cases, being unaffected or only slightly reduced in the others.

Conclusions.

It can therefore be said that:

(1) Penicillin Lozenges do have an effect on the bacterial flora of the fauces, being marked in the case of Strep. pyogenes and Diplo. catarrhalis, and less so in Strep. viridans.

(2) Such effect is apparently independent of the number of lozenges.

EXPERIMENT II.

- Object: What is the time, after administration, of optimum effect of one Penicillin Lozenge, and what is the duration of that effect?
- Subjects: As in Experiment I.
- Method: Four such patients were chosen and throat swabs taken from the surface of both tonsils. Each patient was then given one Penicillin Lozenge, and further throat swabs taken at intervals of $\frac{1}{4}$, $\frac{1}{2}$, 1, 2, 4, 8, 12, 24 and 48 hours, the patients meanwhile eating and smoking as usual.
- Results: See Table II.

TABLE II.

| Organisms - number of colonies before and after the Penicillin Lozenge | | | | | | | | | | | | | | | | |
|--|-----------------|-------------------------------|----|---------------|-----------------|-----|-------|-------|-----------------|-----|-----|-----|--------------------|-----|-------------|---------------|
| Time intervals in hours | Strep. pyogenes | | | | Strep. viridans | | | | Strep. faecalis | | | | Diplo. Catarrhalis | | B. hofmanni | |
| | C a s e s | | | | C a s e s | | | | C a s e s | | | | C a s e s | | | |
| | 21 | 22 | 23 | 24 | 21 | 22 | 23 | 24 | 21 | 22 | 23 | 24 | 21 | 22 | | 23 |
| Before | 65 | 6 | | 2 | 220 | 74 | 800 | 700 | | nil | nil | nil | | nil | nil | 170 |
| After | | | | | | | | | | | | | | | | |
| $\frac{1}{4}$ | 33 | nil | | nil | 210 | 360 | 400 | 40 | | 400 | nil | nil | | nil | nil | nil |
| $\frac{1}{2}$ | 115 | 1 | | nil | 60 | 221 | 400 | 300 | | nil | nil | nil | | 40 | 9 | nil |
| 1 | 44 | 7 | | nil | 600 | 138 | 200 | 350 | | nil | nil | nil | | 40 | 100 | nil |
| 2 | 28 | 3 | | nil | 75 | 300 | 30 | nil | | nil | nil | nil | | nil | nil | 20 |
| 4 | 14 | 12 | | nil | 27 | 50 | nil | nil | | nil | nil | nil | | 10 | nil | nil |
| 8 | 25 | 20 | | nil | 200 | 60 | nil | nil | | nil | nil | nil | | 9 | nil | 3 |
| 12 | 20 | 2 | | nil | nil | 50 | nil | nil | | nil | 100 | nil | | 90 | 2 | nil |
| 24 | 22 | 8 | | nil | 200 | 150 | 300 | 70 | | 150 | 50 | 80 | | nil | nil | nil |
| 48 | 2 | nil | | nil | 15 | 150 | 200 | 400 | | 150 | 600 | 400 | | nil | nil | nil |
| Time of onset | - | $\frac{1}{4}$ | - | $\frac{1}{4}$ | 8-12 | 2-4 | 2-4 | 1-2 | - | - | - | - | - | - | - | $\frac{1}{4}$ |
| Duration | - | $\frac{1}{4}$ - $\frac{1}{2}$ | - | 48+ | 12-24 | ? | 12-24 | 12-24 | - | - | - | - | - | - | - | 1-2 |

From the table it can be seen that:

- (a) If there is any effect it is optimum at

(Strep. pyogenes in 2 of the 3
(15 mins. with) cases,
(B. hofmanni in the only case
(
(2-4 hours with Strep. viridans in 3 of the 4
cases.)

- (b) The duration of such effect seems to vary from

(15-30 mins. to over 48 hrs. in the case of
(Strep. pyogenes.
(1-2 hours in the case of B. hofmanni.
(12-24 hours in the case of Strep. viridans in
3 of the 4 cases.

Results here differ from Experiment I in that Strep. pyogenes in Case 21 is apparently unaffected; and in Case 22 is eliminated but gradually reappears in increasing numbers suggesting rapid lysis of free organisms followed by re-inoculation of the field, possibly from the depths of tonsillar crypts.

Conclusions:

The time of optimum effect is 15 mins. with Strep.
pyogenes, 2-4 hours with Strep. viridans.

The duration of such effect is variable with Strep. pyogenes, 12-24 hours with Strep. viridans.

EXPERIMENT III.

- Object: What is the minimum number of lozenges, given at intervals of 2 hours, required to produce sterility of the fauces, and for how long does that sterile field persist?
- Subjects: As in Experiment I.
- Method: Four such patients were chosen and throat swabs taken from the surface of both tonsils. Each patient was then given four Penicillin Lozenges at intervals of two hours between each lozenge, a throat swab being taken just before the fresh lozenge was given (i.e. two hours after the previous) and at 2, 6 and 18 hours after the last one.
- Results: See Table III.

TABLE III.

| Time intervals in hours | Number of Lozenges given | Organisms - number of colonies before and after the Penicillin Lozenges. | | | | | | | | | | | | | | | |
|-----------------------------|--------------------------|--|-------|-----|-------|-----------------|-------|-------|------|--------------------|----|-------|-----|----|-------|-------|-------|
| | | Strep. pyogenes | | | | Strep. viridans | | | | Diplo. catarrhalis | | | | | | | |
| | | C | | | | A | | | | S | | | | E | | | |
| | | 31 | 32 | 33 | 30 | 31 | 32 | 33 | 30 | 31 | 32 | 33 | 30 | 31 | 32 | 33 | 30 |
| Before | | 23 | 600 | 600 | 600 | 300 | 400 | 800 | 600 | 100 | | 600 | nil | | | | 200 |
| After | 1 | - | 60 | 200 | 200 | 300 | 400 | 800 | 150 | 45 | | 100 | nil | | | 120 | - |
| | 2 | - | - | 6 | 40 | 17 | 120 | 400 | 16 | 4 | | | 200 | | | - | - |
| | 3 | - | - | - | 15 | - | 10 | 200 | - | - | | | 28 | | | - | - |
| | 4 | - | - | - | - | - | - | - | - | - | | | - | | | - | - |
| | 12 | - | - | - | - | - | - | - | 60 | - | | | - | | | - | - |
| | 18 | - | 6 | - | 200 | 6 | 18 | 400 | 120 | 20 | | | - | | | - | 20 |
| | 50 | - | | | | 800 | | | | 150 | | | | | | | |
| Number of Loz. to eliminate | 1 | 1 | 2 | 3 | 4 | 3 | 4 | 4 | 3 | 3 | - | 2 | - | - | 2 | - | 1 |
| Duration | 50+ | 12/18 | 12/18 | 18+ | 12/18 | 12/18 | 12/18 | 12/18 | 8/12 | 12/18 | - | 12/18 | 18+ | - | 12/18 | 12/18 | 12/18 |

From the table it can be seen that:

(a) The minimum number of lozenges required, given at intervals of two hours, to produce sterility of the fauces, was -

(3 lozenges in one of four cases,
(4 lozenges in the other three cases.

(b) The sterile field persisted for -

(2-6 hours in one case out of four,
(6-12 hours in three cases out of four.

Thus in all four cases, four Penicillin Lozenges given at intervals of two hours resulted in a completely sterile faucial field.

Conclusion:

A minimum of four lozenges at intervals of two hours is required to produce sterility, which persists for about six hours.

In view of this result, it was proposed to try out a scheme for pre-operative sterilisation of the operative field for Tonsillectomy.

As patients are admitted to the ward in the evening for operation next morning, the original proposal was a little modified to avoid disturbance of sleep. The proposed scheme consisted of administration of one Penicillin Lozenge at each of 9 p.m., 1 a.m., 5 a.m., 7 a.m., 9 a.m., and tonsillectomy between 9.30 and 12 noon.

Similarly a scheme for post-operative sterility of fauces was proposed, viz., Penicillin Lozenges every two hours from 5 a.m. till 9 p.m., and one during the night (1 a.m.) - total 10 lozenges per 24 hours.

EXPERIMENT IV.

- Object: Having proposed a scheme of administration for attaining sterility of the fauces, is the method effective in practice?
- Subjects: Patients admitted in the evening for Tonsillectomy (dissection) next morning.
- Method: Patient's throat was swabbed on admission. Lozenges were given at 9 p.m., 1 a.m., 5 a.m., 7 a.m., 9 a.m., and the throat swabbed again immediately before operation.
- Results: See Table IV.

TABLE IV.

| Scheme | Case | Organisms - number of colonies before and after Penicillin Lozenges. | | | | | | | |
|----------------|------|--|-------|-----------------|--------|--------------------|------------|---------------|-------|
| | | Strep. pyogenes | | Strep. viridans | | Diplo. catarrhalis | | Staph. aureus | |
| | | Before | After | Before | After | Before | After | Before | After |
| Original | 37 | 270 | - (2) | 200 | - | 50 | - | - | - |
| | 38 | 200 | - | 600 | - | 50 | 600 ϕ | - | - |
| | 39 | 39 | - (8) | 600 | 400 | 72 | 160 ϕ | - | - |
| | 43 | - | - | 70 | 130 | 67 | 4 | 2 | - |
| | 48 | 300 | - | 200 | - (10) | 25 | - | - | - |
| | 53 | 30 | - | 300 | - | 40 | - | - | - |
| | 75 | 50 | - (1) | 600 | - | 300 | - | - | - |
| | 76 | 15 | - | 200 | - | - | - | 150 | - |
| Prolonged | 94 | 800 | - | - | - | 600 | - | - | - |
| | 102 | 30 | - | - | - | - | - | 120 | - |
| | 100 | 100 | - | 600 | 5 | - | - | - | - |
| | 101 | 2 | - | 30 | 25 | - | - | 140 | 80 |
| Elimination in | | 9 of 12 cases | | 7 of 12 cases | | 5 of 8 cases | | | |

Figures in parenthesis (8) represent the number of colonies in the "well" only.

ϕ Bile-resistant growth.

From the table it can be seen that the scheme of premedication resulted in:

Strep. pyogenes (eliminated in 5 of 8 cases,
)
(practically eliminated in the
other 3 cases.

Strep. viridans (eliminated in 5 of 8 cases,
)
(practically eliminated in 1 of
8 cases.

The pre-medication was thus quite satisfactory, but in an attempt to improve it, the period of therapy was prolonged to include administration for a further four hours, the scheme being thus one lozenge at 5, 7 and 9 p.m., 1, 5, 7 and 9 a.m. Thus cases 94, 100, 101, 102, which show:

Strep. pyogenes eliminated in all four cases.

Strep. viridans (eliminated in 1 of 2 cases,
)
(greatly reduced in 1 of 2 cases.

Combining these results we have therefore -

Strep. pyogenes eliminated or practically so in
every one of 12 cases.

Strep. viridans eliminated or practically so in
8 of 12 cases.

Conclusion:

The method is therefore effective especially if slightly prolonged.

EXPERIMENT V.

- Object: Does the Penicillin administered as in Experiment IV sterilize the depths of the Tonsillar crypts as well as the Faucial surface?
- Subjects: Patients admitted in the evening for Tonsillectomy (dissection) next morning.
- Method: Patient's throat was swabbed on admission. Lozenges were then given as in Experiment IV. Throat swab was taken immediately prior to operation. The tonsils after dissection were kept, and, as soon afterwards as possible, the free surface seared with a red-hot glass rod to ensure sterility, the superficial layers to a depth of about 3 mm. sliced off with a sterile scalpel thus exposing the deeper parts of the crypts, and swabs taken one from each tonsil and probing the depths of as many crypts as could be found.
- Results: See Table V.

TABLE V.

| Organisms - Number of colonies before loz., after loz., in Tonsil Crypts. | | | | | | | | | | | | | | | | | |
|---|------|-------------------------|----------------|---------------|---------------|-------------------------|-------|--------|--------|-------------------------|-------|--------|--------|-------------------------|-------|--------|--------|
| Control | Case | Strep. pyogenes | | | | Strep viridans | | | | Diplo. catarrhalis | | | | Staph. aureus | | | |
| | | Before lozenges | After lozenges | Tonsil crypts | Tonsil crypts | Before | After | Tonsil | Tonsil | Before | After | Tonsil | Tonsil | Before | After | Tonsil | Tonsil |
| | | Control - no Penicillin | | | | Control - no Penicillin | | | | Control - no Penicillin | | | | Control - no Penicillin | | | |
| | 40 | | 22 | 12 | 2 | | 400 | - | - | | 300 | - | - | | | | |
| | 45 | | 26 | 4 | 17 | | 100 | - | - | | 4 | 1 | 5 | | 20 | 7 | 50 |
| | 46 | | - | - | - | | 400 | 200 | 400 | | 400 | 10 | 30 | | 200 | 15 | 20 |
| | 49 | | 250 | 400 | 400 | | 400 | 200 | - | | - | - | - | | 120 | 22 | - |
| | 50 | | 60 | 100 | 25 | | 65 | 100 | 25 | | - | 60 | 4 | | 2 | 10 | 8 |
| Treated | 37 | 270 | - (2) | - (7) | 200 | 200 | - | - | - | 50 | - | - | - | | | | |
| | 38 | 200 | - | 4 | 6 | 600 | - | - | - | 500 | 600 | 16 | - | | | | |
| | 39 | 39 | - (8) | -(10) | 80 | 600 | 400 | - | - | 72 | 160 | - | - | | | | |
| | 43 | | | | | 70 | 130 | - | - | 67 | 4 | - | - | 2 | - | - | - |
| | 44 | 18 | | - | - | 400 | | 200 | 200 | 12 | | - | - | | | | |
| | 48 | 300 | - | - | - | 200 | -(10) | - | 40 | 25 | - | - | - | | | | |
| | 53 | 30 | - | - | 400 | 300 | - | - | - | 40 | - | - | - | - | 5 | 600 | 15 |
| | 75 | 50 | -(1) | 10 | 32 | 600 | - | - | - | 300 | - | - | - | - | | | |
| | 76 | 15 | - | - | - | 200 | - | - | - | 10 | - | - | - | 150 | - | 10 | 10 |
| | 94 | 800 | - | - | - | | | | | 600 | - | - | - | | | | |
| | 92 | | | | | | 400 | 400 | - | | 50 | - | - | | | | |
| | 95 | | | 15 | 200 | | | | | | | | | | | 5 | - |
| | 96 | | | | | | | | | | | | | | | 55 | 170 |
| | 97 | | | 50 | - | | | | | | | | | | | 20 | - |
| | 99 | | | 400 | 400 | | | | | | | | | | | - | 400 |
| | 100 | No readings | | | | | 5 | 600 | - | | | | | | | | |
| | 101 | | - | 2 | - | | 25 | 3 | - | | | | | | 80 | 20 | - |
| | 102 | | - | 18 | 20 | | - | - | 400 | | | | | | 20 | 20 | 100 |

From the table, it can be seen that as regards

| | |
|------------------------|---|
| <u>Strep. pyogenes</u> | (control cases show septic crypts (in both tonsils in every case of) 4 with positive throat swabs; (treated cases show septic crypts (in both tonsils in 7 of 14 cases, (in one tonsil in 3 of 14, (sterile crypts in 4 of 14 cases. |
| <u>Strep. viridans</u> | (control cases show septic crypts) in 3 of 5; (treated cases show septic crypts (in 6 of 13. |
| <u>Staph. aureus</u> | (Control cases show septic crypts) in all of 4 cases; (Treated cases show septic crypts (in 8 of 9. |

The only significant difference therefore lies with Strep. pyogenes, none of which appear in the crypts of 4 of 14 cases, although the throat swab before treatment was positive.

Now, although every possible crypt was probed after tonsil section, it is not impossible that one or more crypts, which were the septic focus of that tonsil, were omitted, giving a false negative swab of tonsil crypts.

Again there is the possibility that in these 4 cases the septic focus was elsewhere, say in nasopharynx, and that the tonsil crypts were sterile from the start.

I would also draw attention to the fact that two of the cases received prolonged pre-operative

medication - Case 75 for three days, Case 76 for four days, and yet both cases still show septic crypts.

Conclusion:

Thus Penicillin apparently does not sterilize the depths of the Tonsillar crypts as well as the faucial surface, whether it be given as in Experiment IV, or over a much longer period.

EXPERIMENT VI.

Object: Having proposed a scheme of administration for attaining post-operative sterility of fauces, is the method effective in practice?

Subjects: As in Experiment IV.

Method: Patient's throat was swabbed on admission. After dissection of tonsils, Lozenges were given every two hours, 5 a.m. till 9 p.m., and one at 1 a.m. (Control cases received no lozenges.) Tonsillar fossae were swabbed at the stated time after operation.

Results: See Table VI.

TABLE VI.

| Case | Duration of Treatment Hours | Organisms - colony counts before & after Tonsillectomy + P. Iozs. | | | | | |
|----------------|-----------------------------|---|------------------|-----------------|-------|--------------------|-------|
| | | Strep. pyogenes | | Strep. viridans | | Diplo. catarrhalis | |
| | | Before | After | Before | After | Before | After |
| 13 | | 12 | - | 80 | 600 | - | 600 |
| 20 | | - | 60 | 1000 | 700 | 200 | 150 |
| 26 | | 120 | 600 | 400 | 800 | 400 | 600 |
| 28 | | | - (8) | 800 | 400 | - | 150 |
| 40 | | 22 | - (8) | 400 | 70 | 300 | 250 |
| 45 | | 26 | - | 100 | 400 | 34 | 600 |
| 46 | | | | 400 | 600 | 400 | 400 |
| Elimination in | | 2 of 6 cases | | None of 7 cases | | None of 7 cases | |
| 12 | 50 | 600 | - | 600 | - | 400 | - |
| 19 | 50 | 8 | - | 40 | - | 200 | - |
| 25 | 56 | 26 | - | 400 | - | 400 | - |
| 27 | 52 | | | 600 | - | 600 | 35 |
| 29 | 52 | | | 150 | - | | 26 |
| 37 | 48 | 270 | 600 ^ø | 200 | - | 50 | - |
| 38 | 70 | 200 | - | 600 | - | 50 | - |
| 39 | 70 | 39 | - | 600 | - | 72 | - |
| 43 | 72 | | | 70 | - | 67 | - (2) |
| 44 | 72 | 18 | - | 400 | - | 12 | 400 |
| 48 | 72 | 300 | - | 200 | - | 25 | 20 |
| 53 | 78 | 30 | - | 300 | - | 40 | 5 |
| Elimination in | | 8 of 9 cases | | 12 of 12 cases | | 8 of 11 cases | |
| | | | | | | 5 of 5 cases | |

^øThis throat was shown to be sterile prior to operation but became reinfected.

From the table it can be seen that -

- (a) Control series - Tonsillectomy alone resulted in no sterile tonsillar fossae in 7 cases.
- (b) Treated series - Tonsillectomy then Penicillin resulted in sterile fossae in 8 of 12 cases; practically sterile fossae in 11 of 12 cases.

Conclusion:

The method of attaining post-operative sterility of fauces is thus very effective in practice and can maintain sterility for 50-78 hours at least, and probably for as long as desired if medication is continued.

RESUME of CONCLUSIONS in CHAPTER II.

Experiment I.

Conclusion: Penicillin Lozenges do have an effect on the bacterial flora of the fauces, being marked in the case of Strep. pyogenes and Diplo. catarrhalis and less so in Strep. viridans, such effect being apparently independent of the number of lozenges.

Experiment II.

Conclusion: Time of optimum effect is 15 mins. with Strep. pyogenes, 2-4 hours with Strep. viridans, the duration of that effect being variable with Strep. pyogenes, 12-24 hours with Strep. viridans.

Experiment III.

Conclusion: A minimum of 4 lozenges at intervals of 2 hours is required to produce sterility, which persists for about 6 hours.

Experiment IV.

Conclusion: Administration of lozenges at 5, 7, and 9 p.m., 1, 5, 7, and 9 a.m. is a practical method of attaining sterility of the fauces overnight.

Experiment V.

Conclusion: Administration of Penicillin lozenges does not sterilize the depths of the Tonsillar crypts.

Experiment VI.

Conclusion: Administration of Penicillin Lozenges every 2 hours during the day, and once at night (10 lozenges per 24 hours) is a practical and effective method of maintaining sterility of fauces.

Consider the findings as regards Strep. pyogenes, the principal pathogen. After administration of one Penicillin Lozenge, elimination of Strep. pyogenes for at least 2 hours was attained in 4 out of 8 cases (see Tables I-III), while after 4-5 lozenges elimination for at least 2 hours was attained practically in every one of 12 cases (see Tables I, III & IV).

Thus 4-5 lozenges, and not one, are required to ensure elimination of Strep. pyogenes.

In view of these conclusions on a Bacteriological basis, I decided to go ahead with a clinical trial of the efficacy of Penicillin Lozenges in the treatment of Tonsillectomy and its sequelae, Acute Streptococcal infections, and Vincent's infection.

CHAPTER III.CLINICAL TRIALS.

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CHAPTER III.Para (1) TONSILLECTOMY.

Tonsillectomy is the commonest operation performed in any Ear, Nose and Throat Hospital. Its indications are numerous and varied, and need no discussion here. It may be performed by Guillotine, or by Dissection under local or general anaesthesia. The following account concerns only cases done by Dissection.

The operation involves incision of intact epithelium but differs greatly from operations on other surfaces (e.g. skin) in that no attempt whatever is made to prepare the field for operation and the wound is made and left to heal in a septic, or potentially septic, cavity, the throat.

Removal of the tonsils leaves between the pillars a fairly large area of traumatised tissue which is stimulated to proliferate, and the tonsil-bed begins to heal as does any open wound, namely by filling up of that gap from below by granulation tissue, built on the scaffolding of coagulated blood, fibrin and inflammatory exudate which filled it immediately after operation, which tissue later becomes organised and converted into fibrous tissue, while epithelium grows

over its surface and closes the gap. In time that fibrous tissue contracts to form dense scar tissue. At the same time there is mortal conflict between bacterial invasion, by the commensals and pathogens of the oral cavity, and the body's defences in the form of leucocytes and antibodies, which attempt to localize any infection. Not until the leucocytes have overcome the infection does the epithelium begin to cover the surface and healing commence (Boyd, 1938). Upon the intensity and duration of this battle therefore depend the amount of slough and granulation formation, local inflammatory reaction and pain in the first few days after operation, and hence the degree of scarring and contraction of the tonsil bed with the possibility of impairment of faucial mobility if these be great.

Anything therefore that we can do to influence the outcome of this battle will be of great service to the patient. As far as the general and local resistance of the patient is concerned, there is little that can be done in the four or five days that he remains in hospital. Any possible improvement rests then in an attempt to control the infective factor.

It was in view of these facts, and of the excellent results of the experiments (in Chapter II) in controlling faucial infection, that it was decided to investigate the clinical effect of administration of

Penicillin locally to patients before and after Tonsillectomy.

The usual course of events includes some degree of pain, that of the first day or so being the result of operative trauma, but of subsequent days, if present, due to infection of the tonsil bed clinically apparent by the flushing and oedema of the anterior pillar and soft palate, the excessive dirty slough formation, and relative immobility of the fauces. Routine treatment consists of gargles and sedatives, local or general, with exhibition of sulphonamides should there be any constitutional disturbance.

Granulations have fully formed and slough begun to separate by the fifth day and the process continues to complete separation, leaving a clean healing fossa by the eighth-tenth day, apart from small areas of slough around the sites of ligatures which take a little longer to separate. If the slough has been very deep and extensive there is the danger of secondary haemorrhage during this period.

As all the observations in this series were to be clinical (apart from those on whom incidental bacteriological study was made), I required a routine method of examination which would reveal the criteria for comparison of the treated and control cases.

The scheme was as follows:-

Patients for Tonsillectomy were admitted to the ward either on the evening before or on the morning of their operation, the former receiving Penicillin therapy, and the latter being used as controls.

Those receiving Penicillin were given their lozenges according to the schemes in Experiments IV and VI before and after operation respectively, and had no other treatment. The controls received only routine post-operative supervision, gargles, and sedatives.

All the patients were examined on the third morning after operation, allowed home, and returned for further examination on the eighth morning, and final inspection at four-six weeks after operation. At each visit records of examination were made on the following basis - the examiner being ignorant as to whether or not the patient had received any Penicillin treatment.

On the fourth and ninth days -

- (1) The condition of the pillars, whether normal in colour and texture, or flushed and oedematous of variable degree; bruising of pillars and palate and oedema of uvula were also noted as indicative of the degree of operative trauma and its reaction, factors which might influence the result.

- (2) The thickness and consistency of slough formation measured as -, ±, +, ++, +++, noting its stage of separation as mobile, slightly, or firmly fixed.
- (3) The degree of pain suffered, judged rather arbitrarily as -, ±, +, ++ or +++ by questioning the patient.

After four to six weeks -

- (1) The condition of the pillars, whether normal in form and movement, or submerged or thickened: also whether mobile or fixed by scar tissue.
- (2) The condition of the tonsil-bed as regards slough or granulations still present, or healed: as regards scarring and fibrosis by -, ±, +, ++, +++. .
- (3) Contracture of the faucial arch as -, ±, +, ++, +++, with special regard to distortion of the uvula and fixity to the tongue margins.

Three different series were done, and are reported separately.

- A. Received Penicillin after operation only, and for three days.
- B. Received Penicillin before and after operation, the latter for three days.
- C. Received Penicillin before and after operation, the latter for eight days.

Simultaneously those patients arriving on the morning of operation received no Penicillin, and constitute the control series D.

The results are expressed in tabular form hereafter. For the sake of clarity in the tables, a system of symbols representing the clinical conditions found has been formulated and is given below. In addition, in order to summarise the results more easily a system of points was adopted, the greater points being allocated to the more severe conditions, e.g. in considering the slough on the tonsil bed on 4th and 9th days the thickness and consistency is recorded by plusses each counting one point, and the degree of separation by F = fixed = 2 points, f = slightly fixed or commencing separation = 1 point, M = Mobile and separating = 0 points.

| | | |
|-------------------|---------------------------|----------------------|
| Br = Bruised (0) | br = slightly bruised (0) | |
| F = fixed (2) | f = slightly fixed (1) | M = Mobile (0) |
| Fl. = flushed (2) | fl = slightly flushed (1) | N = normal (0) |
| | h = not quite healed (1) | H = healed (0) |
| | O = oedema (1) | Tg = Tongue adherent |
| | S = submerged (1) | U = Uvula |
| | T = thickened. | |

These figures are totalled at the foot of the respective columns and give a fairly accurate reckoning of the number of cases in which that feature appears, and as a decimal fraction help to describe the average case. The gaps are due to the failure of some patients to report for examination.

TABLE VII.

Series D (Controls): 32 Cases.
Patients receiving no Penicillin.

| Case | On 4th Day | | | On 9th Day | | | After 4-6 weeks | | | | | |
|----------------|------------|---------|-------|------------|---------|-------|-----------------|----------|-------------|----|--|--|
| | Pillars | Slough | Pain | Pillars | Slough | Pain | Pillars | Scarring | Contracture | | | |
| 3 | fl | ++ f | + | N | \pm M | - | S M | H + | + | | | |
| 13 | Fl | ++ F | ++ | N | + f | \pm | | | | | | |
| 20 | Fl O Br | +++ F | +++ | fl | + f | + | T M | H + | + | | | |
| 26 | Fl O | ++ F | \pm | | | | T f | H +++ | ++ | | | |
| 28 | fl Br | +++ F | \pm | N br | ++ f | + | T F | H ++ | +++ Tg | | | |
| 40 | Fl O | +++ F | + | N | ++ f | - | S f | H ++ | ++ U | | | |
| 45 | N | ++ F | + | N | \pm M | - | S f | h + | ++ | | | |
| 46 | fl Br | +++ f | + | | | | ST M | H ++ | +++ | | | |
| 49 | Fl O | +++ F | + | N | + f | - | S f | h ++ | ++ U | | | |
| 50 | fl | +++ F | + | | | | | | | | | |
| 52 | fl Br | +++ F | ++ | | | | S | h + | ++ Tg | | | |
| 54 | | | | | | | N M | H + | + | | | |
| 56 | Fl br | ++ F | + | N | - | + | S | H + | - | | | |
| 57 | Fl O | + F | ++ | fl | + M | + | T M | H + | ++ Tg | | | |
| 58 | fl | ++ f | +++ | fl | - M | ++ | N M | H + | - | | | |
| 59 | Fl br | +++ F | ++ | fl | \pm f | ++ | N f | H + | + | | | |
| 60 | Fl Br | +++ F | ++ | | | | ST F | H +++ | + | Tg | | |
| 62 | | | | | | | N f | H \pm | ++ Tg | | | |
| 70 | Fl O | +++ F | +++ | | | | S M | H \pm | - | | | |
| 71 | fl O | ++ F | ++ | | | | | | | | | |
| 74 | Fl O | ++ F | + | fl | - | \pm | N M | H + | \pm Tg | | | |
| 84 | Fl | + F | + | N | - | - | | | | | | |
| 85 | Fl O U | + F | ++ | | | | S F | H +++ | ++ Tg | | | |
| 86 | Fl O | ++ F | +++ | N | - | \pm | S f | H + | - | | | |
| 88 | Fl U | ++ M | + | fl | ++ M | ++ | s f | H ++ | - | | | |
| 89 | Fl O U | + f | + | | | | T f | H + | - | | | |
| 90 | Fl O | + f | + | | | | | | | | | |
| 91 | Fl O | ++ F | ++ | | | | S f | H ++ | - Tg | | | |
| 114 | fl Br | +++ F | ++ | fl | \pm | - | N M | H ++ | - Tg | | | |
| 115 | fl br | ++ F | + | fl | \pm | \pm | S M | H - | + | | | |
| 118 | Fl | ++ F | + | fl | \pm | - | N M | H - | - | | | |
| 120 | Fl O U | ++ F | ++ | Fl | + M | + | | | | | | |
| Total Points | 49 14 | 66 53 | 47 | 11 | 14 6 | 13 | 20 16 | 3 36 | 26 11 | | | |
| Average Points | 2.1 | 2.2 1.8 | 1.6 | .6 | .75 .3 | .7 | .8 .6 | .13 1.4 | 1.0 | | | |

TABLE VIII.Series B: 25 Cases.

Patients receiving Penicillin for 12 hours before,
and 3 days after operation.

| | On 4th Day | | | | On 9th Day | | | | After 4-6 Weeks | | | | | | |
|----------------|------------|----|--------|-----|------------|---------|----|--------|-----------------|------|---------|----|----------|-----|-------------|
| Case | Pillars | | Slough | | Pain | Pillars | | Slough | | Pain | Pillars | | Scarring | | Contracture |
| 38 | fl | | + | M | + | N | | ± | M | - | S | M | H | ++ | ± |
| 39 | fl | | + | M | + | N | | ± | M | - | T | M | H | ± | ± |
| 43 | N | Br | ++ | M | | | | | | | | | | | |
| 44 | N | | - | | - | | | | | | N | M | H | - | - |
| 48 | fl | | ++ | M | ± | N | | ± | | - | T | | h | + | + |
| 53 | N | | + | M | + | N | | - | | - | N | M | H | - | - |
| 63 | fl | | + | M | +++ | | | | | | T | M | H | ++ | + |
| 64 | fl | Br | - | | ± | | | | | | N | M | H | ± | - |
| 65 | N | br | - | | ± | | | | | | S | M | H | ++ | + |
| 66 | N | | ± | M | - | | | | | | | | | | |
| 68 | fl | | + | M | + | Fl O | | +++ | F | + | S | F | h | +++ | ± |
| 69 | fl | | + | M | + | N | | - | | - | N | M | H | + | - |
| 72 | fl | | ± | | + | fl | | ± | | ± | | | | | |
| 73 | fl | br | ++ | F | + | fl | | ± | | - | S | f | H | + | + |
| 75 | | | | | | N | | ± | | ± | | | | | |
| 76 | | | | | | N | | + | M | ± | | | | | |
| 77 | N | br | - | | ± | N | | ± | | ± | N | M | H | + | - |
| 78 | fl | Br | + | f | + | fl O | | ++ | F | + | N | M | H | + | ± |
| 79 | fl | | - | | ± | | | | | | S | M | H | + | ± |
| 80 | | | | | | N | | ± | M | + | | | | | |
| 81 | N | Br | ± | | ++ | N | | - | | - | N | M | H | + | - |
| 82 | Fl | | + | F | + | fl | | - | | ± | N | f | H | + | + |
| 83 | fl | U | + | M | + | N | | - | | ± | S | F | H | ++ | ++ |
| 87 | N | | + | M | ± | | | | | | N | M | H | + | - |
| 93 | | | | | | N | | - | | - | N | M | H | + | - |
| Total Points | 14 | 0 | 17.5 | 5 | 18.5 | 6 | 2 | 9 | 4 | 6 | 9 | 6 | 2 | 22 | 9.5 |
| Average Points | .66 | | .8 | .25 | .8 | .4 | .1 | .5 | .2 | .4 | .5 | .3 | .1 | 1.2 | .5 |

TABLE X.

Series C: 13 Cases.
 Patients receiving Penicillin for 16 hours before,
 and 8 days after operation.

| Case | On 4th Day | | | | On 9th Day | | | | After 4-6 Weeks | | | |
|----------------|------------|--------|------|----|------------|--------|------|---|-----------------|----------|-------------|----|
| | Pillars | Slough | Pain | | Pillars | Slough | Pain | | Pillars | Scarring | Contracture | |
| 94 | fl | + | M | - | N | M | + | M | | | | |
| 95 | N | + | M | ± | N | M | - | - | | | | |
| 96 | N | + | M | + | N | M | - | - | N | H | - | |
| 97 | N | + | M | - | | | | | S | f | + | |
| 98 | N | - | | ± | N | | - | ± | N | M | - | |
| 99 | N | ± | | - | N | | - | ± | S | M | - | |
| 100 | N | + | f | + | N | | - | - | N | M | - | |
| 101 | N | + | M | + | N | | - | ± | N | M | +++ | |
| 102 | N | - | | + | N | | - | - | N | M | + | Tg |
| 121 | N | ± | M | - | N | | ± | - | S | f | + | Tg |
| 122 | N | ± | M | - | N | | ± | - | | | | |
| 125 | N | ± | M | - | N | | ± | - | | | | |
| 127 | fl | + | M | + | N | | - | + | N | M | - | |
| Total Points | 2 | 10 | 1 | 9 | 0 | 2 | 3 | | 3 | 2 | 0 | 4 |
| Average Poinrs | .2 | .8 | .1 | .7 | | .2 | .3 | | .3 | .2 | 0 | .4 |

Consider the condition on the fourth day.

In Series D (Control) the average cases show flushed pillars with a little oedema, slough ++ which is fixed and showing no signs of separation, and pain + to ++.

Series A (post-op. only) at once shows a marked difference. Slightly flushed pillars are present in only half the cases: slough is + and separating in nearly every case, and pain is +.

Series B (short pre- and post-op.) shows greater improvement still with slight flushing in two thirds of cases, but slough less than +(0.8) and separating in three fourths of cases, and pain less than +.

Series C (long pre- and post-op.) shows the best results of all, with slight flushing of pillars in only two of thirteen cases, slough + in ten and separating in nine of these, with pain less than + on the average.

Series A, B and C all had lozenges up to the time of examination on the fourth day, the difference lying only in the pre-operative dosage which was nil in A, spread over 12 hours in B, and over 16 hours in C.

From these results it can be seen that local

Penicillin as a post-operative measure results in a rapid and marked alleviation of the local condition: and that the longer the pre-operative medication the greater is that improvement.

Consider the condition on the ninth day.

In Series D (Control), 11 of 19 cases show slight flushing of pillars, with on the average less than slough + which is separating in 13 of 19 cases, and less than pain +.

Series A (post-op. only) shows normal pillars with less than slough + and no pain, but unfortunately only three cases are available for comparison.

Series B (short pre- and post-op.) shows slight flushing of pillars in only 6 of 17 cases and oedema in 2, slough + in 9 and separating in 5 of these, with pain + in only 6 of 17 cases.

Series C (long pre- and post-op.) reveals remarkable improvement with normal pillars in every one of ten cases of which only two show slough + (and that separating) and pain +.

Consider the condition after 4-6 weeks.

Series D (Control) shows normal pillars in only 6 of 26 cases, full mobility in 11, complete

healing in all but three cases, scarring ++ in three-fourths of the tonsil-beds, contracture ++ in half and some other adhesion in 11 of 26 cases.

Series A (post-op. only) averages normal pillars in 1 of 4, but full mobility in 3 of 4, with healing in every case, scarring ++ in half the cases and contracture in less.

Series B (Short pre- and post-op.) averages normal pillars in 10, with full mobility in 14 of 19 cases, healing in all but 2, scarring ++ in 11 of 19 cases and contracture in half of them.

Series C (long pre- and post-op.) averages normal pillars in all but 3, with full mobility in all but 2 of 9 cases, healing in every case, scarring ++ in half the cases and contracture in less.

These results may be summarised in tabular figures:-

TABLE XI.

| | On 4th Day | | | | On 9th Day | | | | After 4-6 Weeks | | | | Grand Total |
|---|------------|--------|------|--------------|------------|--------|------|--------------|-----------------|----------|-------------|--------------|-------------|
| | Pillars | Slough | Pain | Total Points | Pillars | Slough | Pain | Total Points | Pillars | Scarring | Contracture | Total Points | |
| D | 2.1 | 4.0 | 1.6 | 7.7 | .6 | 1 | .7 | 2.3 | 1.4 | 1.5 | 1.0 | 3.9 | 13.9 |
| A | 0.5 | 1.2 | 1 | 2.7 | 0 | 0.6 | 0 | 0.6 | 1.0 | 1.0 | 0.9 | 2.9 | 6.2 |
| B | 0.7 | 1.1 | 0.8 | 2.6 | 0.5 | 0.8 | 0.4 | 1.7 | 0.8 | 1.3 | 0.5 | 2.6 | 6.9 |
| C | 0.2 | 0.9 | 0.7 | 1.8 | 0 | 0.2 | 0.2 | 0.4 | 0.5 | 1.0 | 0.4 | 1.9 | 4.1 |

From these it can be seen that, ignoring the results of series A at 9th day, since these were judged from only three cases, there is progressive improvement as the duration of Penicillin therapy is increased, i.e. best results are obtained with the longer pre-operative medication and prolonged treatment after operation.

Also it is seen that there is a much more striking difference at the 4th day (7.7 to 1.8) and 9th day (2.3 to 0.4) than after the throat has healed (3.9 to 1.9), i.e. the beneficial effect of local Penicillin therapy lies more in the immediate post-operative period than in the final result, more in the anaesthetic (by prevention of the pain of sepsis) than the aesthetic field.

Several cases are of individual interest.

Cases 68 and 78 (Series B) showed good average throats when seen on the 4th day. Five days later, however, having had no Penicillin in the interval, they had relapsed to a state of affairs worse than on the 4th day through infection supervening after stopping the Penicillin and before the wound was sufficiently healed.

Cases 72 and 77 (Series B) are somewhat similar in that after good progress up to the 4th day, the



condition thereafter remained static without the progressive improvement seen in all other cases.

These examples only go further to show that best results are to be obtained by prolonging the Penicillin for as long as practicable. None of the 13 cases in Series C show any tendency to such relapse, suggesting that a duration of nine days is adequate.

Again in Series C, cases 100 and 101 showed considerable slough and pain even on the 4th day, but were completely clear and painless on the 9th, demonstrating the advantage of continuing the therapy. On the other hand several throats (Cases 94, 98, 121, 122) were practically as clear on the 4th as on the 9th day.

SUMMARY and CONCLUSIONS in CHAPTER III, Para (1).

The normal process of healing after tonsillectomy is described with reference to factors causing delay, upon which the local use of Penicillin might have some influence.

The scheme of administration and system of examination used in this investigation into the use of Penicillin in Tonsillectomy and its sequelae is proposed, there being three treated and one control series.

Individual results are detailed in tabular form, and by a system of points summarised to depict what would be the average case.

It is concluded that the beneficial effect is more immediate post-operative than terminal, more anaesthetic than aesthetic, and that this effect is most marked with prolonged medication as exemplified by a few selected cases.

CHAPTER III.

Para (2)

VINCENT'S INFECTION.

CHAPTER III.Para (2) VINCENT'S INFECTION.

Vincent's Angina, Ulcero-Membranous Stomatitis or Fusio-spirochaetosis is a superficial ulceration necrosis which may involve the tonsils, gums or buccal mucosa as an acute or chronic infection in each situation.

In spite of years of research, the aetiology is still obscure. Originally ascribed to the predominant organisms found, namely a combination of Bacillus Fusiformis and Spirochaeta Vincenti, it is now realised that these organisms are more probably secondary invaders which merely proliferate in necrotic tissue, opportunists rather than primary pathogens, but which soon become the primary issue. These organisms are present, though scanty, in 21% of normal mouths, and in 32% of cases of faucial infection (Smith and Stewart, 1942). Others have regarded it as a multiple infection including the various streptococcal and cocci infections (Jones, 1945; Smith, 1932).

The problem therefore lies in the discovery of the predisposing factors which permit such harmless saprophytes to become pathogenic. Such factors may be general, as in conditions of lowered health and resistance, even by such a temporary ailment as the

common cold (King, 1943), or of hypo-vitaminosis B, especially of Nicotinic Acid (King, 1940) (although such deficiency produces the characteristic evidence in the mouth only when teeth are present (Stobie, 1943), implying some local factor also); or local as in lack of oral hygiene, food stasis, erupting teeth, irregularities of teeth or of fillings, retained roots, dental caries (Moir, 1942), extractions (although the chronic trauma of an erupting third molar is more likely to reduce resistance than the acute condition after extraction (Longhurst, 1943)). It is obvious therefore that the onset can be attributed to no single factor.

The stage having thus been set for invasion by Vincent's and other organisms, the initial lesion is undoubtedly a gingivitis, in consideration of the above local factors and of the observation that Vincent's Angina seldom, if ever, occurs in the absence of gingivitis, the original seat of infection (McKinstry, 1917), although there too local factors come under review in that it is rare for Vincent's Infection to attack a healthy tonsil (Smith and Stewart, 1942).

Others have taken an entirely different line of thought in regarding the Herpes Simplex Virus as the

primary aetiological agent, as proved by satisfaction of Revers' criteria for virus aetiology (Black, 1942), but this epidemic gingivo-stomatitis "seems to be of a different character from that with which we are familiar and in which the spirochaete and fusiformis predominate" (Longhurst, 1943).

Pathologically it appears that the organisms do not penetrate very deeply from the surface, since the tissues just below appear clinically normal, and produce their rapidly spreading necrosis by virtue of being highly fibrolytic by themselves or in conjunction with other bacteria (Fish, 1938).

Clinical diagnosis, perhaps suggested as the patient approaches by the marked foetor of the acute stage, rests on the characteristic ulcero-membranous destruction, rapidly spreading when acute, with a slight and localised halo of inflammatory reaction, cervical adenitis often quite severe, but little or no constitutional disturbance. When chronic, the condition may be almost symptomless or associated with complaint of slight dysphagia in the presence of a quietly spreading crater ulcer of one or both tonsils, or of bleeding gums when the dental sulci are filled with yellowish debris, and the gums fleshy, soft, and swollen.

Diagnosis is confirmed by direct smear, stained with methyl violet, and made in a matter of minutes: culture reveals a motley collection of organisms, mainly non-haemolytic streptococci and staphylococci. Great care however is necessary to exclude other clinically similar conditions such as Faucial Diphtheria, Syphilis, Tuberculosis, Malignancy, Anginous Glandular Fever, Agranulocytosis, etc., in any of which there may be a secondary infection with Vincent's organisms.

Diagnosis then essentially depends on correlation of clinical and laboratory findings.

Treatment of this condition in the past has been by very many and varied methods, the very multiplicity of which implies their lack of success. In fact one recent text book (Dunlop, Davidson, McNee and others, 1942) goes so far as to say that "no certain rapid cure of the disease is known, but recovery may be expected in most cases in a week or ten days". Any rationale of treatment must first control and eradicate the immediate infection-ulceration, and second attempt to discover the predisposing factors and by eliminating these reduce the liability to recurrence.

With its known effect upon spirochaetes, arsenic has always been a favourite remedy, applied locally as

Liquor Arsenicalis or as one of the organic preparations, and perhaps alternated with daily paintings with an iodine preparation; systemically as intravenous organic arsenic, advocated as specific treatment in the initial stages and repeated if required.

Various authors (Sutton, 1924; Hillsman and Driscoll, 1925; Williams, 1929; Donson, 1933; Goodridge, 1942) have recorded isolated cases of Vincent's infection occurring during treatment of syphilis with intravenous arsenic, and others (Reichmann, 1926; Farrell and McNicholl, 1937; Jewesbury, 1944) groups of similar cases; two similar cases are quoted in the series appended. If then such infection can develop in patients receiving as it were massive prophylactic doses, surely it is unsound therapy. Besides, intravenous therapy is not without risks, especially of so called post-arsphenamine jaundice now known to be of viral origin. Animal experiments (Rosebury and Foley, 1939) have proved the futility of intravenous neoarsphenamine but showed that locally applied it produced "distinct amelioration".

Local application of oxidising agents, to counter infection by these anaerobic organisms, has found great favour, such treatment being equally effective as and immensely cheaper than local application of

arsenic. These include hydrogen peroxide, zinc peroxide, sodium perborate, and chromic acid, often used in combination such as daily swabbing with 10-20% chromic acid followed by peroxide in addition to peroxide mouth-washes every two hours (Moir, 1942; Jewesbury, 1943). Healing of the acute ulcerative type in an average of four days is claimed (King, 1943). Others, using zinc peroxide powder spray, have claimed more rapid relief of pain, ulceration and foetor, and cure in an average of seven days as compared with 12.5 days in a control series (Nizel and Rubin, 1943).

Dye antiseptics such as acriflavine, gentian violet, and brilliant green have also been used.

Vitamin C was formerly suggested as a possible deficiency but examination has shown absence of any relation between lack of saturation with this vitamin and incidence of the disease (Stobie, 1943), and clinical trial of treatment with ascorbic acid has proved useless (King, 1943).

Since however Vincent's infection was associated with a pre-pellagrous state (King, 1940), good results (King, 1943) have been reported with nicotinic acid therapy (50 mgm. t.i.d.) which, used alone in the acute ulcerative form, gave healing in five days, and,

combined with local chromic acid and peroxide as above, in an average of two days, limit four days. Sulphonamides, notably sulphathiazole, have been used with benefit despite the insensitivity of the spirochaete. Given systemically (orally) in gingivitis in doses of 1 gm. q.i.d., it will give symptomatic relief in 24 hours with a striking decrease in the number of Vincent's organisms, and in angina in full doses it will produce subsidence of peritonsillar inflammation and smears showing only occasional spirochaetes on the fourth day (Hirsch and Spingarn, 1943). It has also been used locally as a tablet dissolved on the tongue, $\frac{1}{2}$ gm. every two hours by day, 1 gm. every four hours by night, giving improvement in 24 hours, practical absence of symptoms in 48 hours, and clinical recovery in 72 hours (Linton, 1943). Used incorporated in chewing gum it has produced a decrease in the total count in 67% of cases within 48 hours (Fox, Kesel, Neary and Herbine, 1945).

Recent criticism of treatment (Nimmo Smith and Stewart, 1942) has been that in the case of a Vincent's angina, infection is apt to lurk in the crypts giving a negative smear, so that test for cure is uncertain. In view of this, and of the fact that it is rare for Vincent's to attack a healthy tonsil, the suggested

treatment is tonsillectomy in the acute stage, one day after admission and treatment with I.V. arsenic and local Brilliant Green. Acriflavine and sulphanilamide powder are used as precautions during and immediately after operation.

Infectivity and transmission of Vincent's Infection has always been assumed and there are some recorded cases of its local epidemicity through use of communal mugs or water-dipper (Stobie, 1943), although it was found that to implant the organisms into a healthy mouth caused no infection (King, 1940) - evidently other factors besides infection are necessary.

It was in face of this unsatisfactory position - the different methods of treatment, the complexity of some and time-consuming labour of others, the degree of discomfort to the patient and variability in end-results - that it was decided to investigate the local use of Penicillin in Vincent's Infection.

The therapy adopted consisted of lozenges (agar, as described elsewhere) to be retained in the mouth, one such being given every two hours. All cases except one were treated as out-patients. No other treatment, such as gargles or mouth-washes, was used

in any case.

I will report some cases in detail. (Summary, p.83)

Case 1. Mrs M. S., 29 years. Acute Vincent's
Angina of Pharynx.

Complaint of sore throat for several days.

Examination: Bulging of right pharyngeal wall with
extensive necrotic area on the summit.
Swab revealed Vincent's organisms: Strep.
viridans on culture.
W.R. and Kahn negative.

Treatment:

Local - daily painting with Liquor Arsenicalis
for 11 days.
Intravenous Neoarsphenamine) (0.15 gms. on
first day,
(0.3 gm. on
(fourth day.

On 12th day - healing satisfactory.

19th day - recurrence of sloughing: Liq.
Arsenicalis paint 3x/wk.

36th day - Satisfactory.

Comment: Combined local and general arsenicals
resulted in apparent cure by 12th day, but re-
lapse a week later and final cure after one
month.

Case 2. Pte. R. M., 19 years. Chronic Vincent's
Angina of Tonsil.

No complaints: Crater ulcer of right tonsil with
considerable loss of tissue, found on routine
examination. Swab - Vincent's organisms.

Treatment: Local ^{liq.}arsenicalis paint daily, to
tonsils.

On 25th day little improvement of right tonsil, and meanwhile infection has spread to involve left tonsil and lower gums, with considerable sloughing.

Comment: Local arsenic alone resulted in little or no local improvement, while infection was all the time spreading further.

Case 3. Miss E. R., 15 years. Acute Vincent's Angina, Dental and Buccal.

Complaint of painful bleeding gums for one week, and ulcerated swollen cheek for two days: bad breath.

Examination revealed inflamed, spongy, bleeding gums especially in the region of right molars (upper and lower) where the teeth were rather carious and 6} frankly necrotic; slough in dental sulcus there and at lower incisors. Buccal mucosa adjacent swollen, raw and bleeding, and covered with a dirty grey slough. Oedema of cheek externally. Submandibular adenitis. Foetor marked.

Swab: direct film revealed Vincent's organisms + + + +, approximately 50 of each per micro-field (Plate I).

Treatment: Penicillin Lozenges 2-hourly.

After 48 hours - symptomatically greatly improved; now no pain, tenderness, nor foetor.

Examination revealed firm pink gums which

did not bleed on pressure, slight debris in dental sulci. Buccal mucosa clean, slightly granular, no slough. No oedema: glands no longer tender. No foetor.

Swab: direct film - no Vincent's organisms to be found (Plate II).

After 96 hours - symptomatically cured.

Examination - gums and buccal mucosa smooth, pink and healthy.

No recurrence to date - three months.

Comment: Rapid dramatic cure within four days, probably less, with the minimum of trouble and supervision.

Bacteriological cure in 48 hours.

Case 4. Mrs V. V., 32 years. Acute Vincent's Angina of Left Tonsil.

First seen in V.D. Department on 25.1.45 as pregnancy complicated by W.R. +++. Treated by unit course of seven injections totalling Stabilarisan 1.05 gm. and Bioglucol 0.7 gm.: last injection on 24.2.45.

1.3.45: Ulceration of throat, painted with chromic acid.

6.3.45: Abortion.

8.3.45: First seen, when examination revealed -

Left tonsil enlarged, completely covered with dirty grey slough: marked loss of tissue: diffuse deep flush of surrounding palate: painful adenitis on left

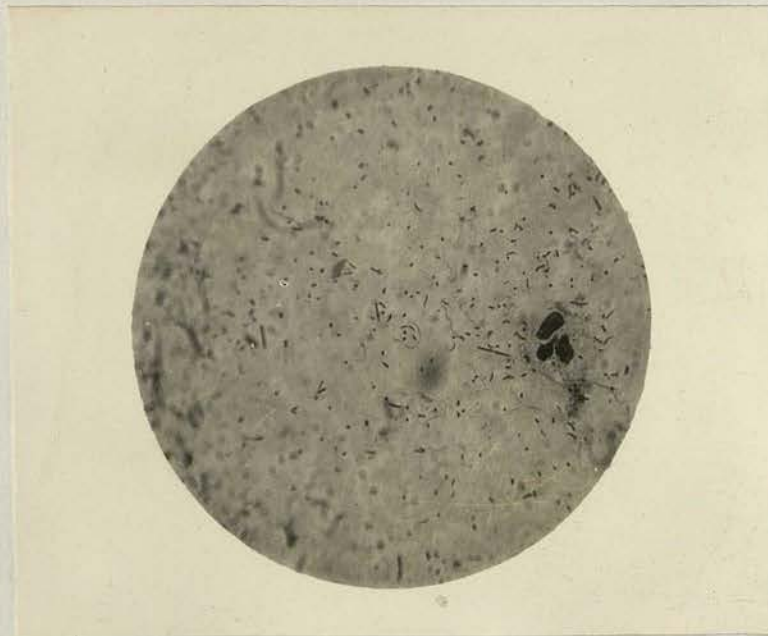


Plate I.

Case 3. E.R. Smear taken when first seen, showing B. Spironema Vincenti and B. fusiformis in profusion (about 50 per field), also some cocci.

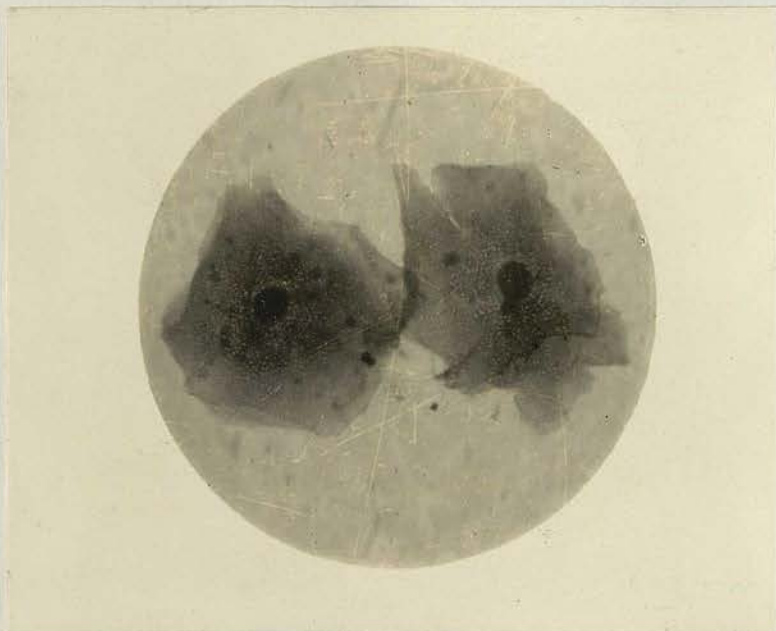


Plate II.

Case 3. E.R. Smear taken after 48 hrs. therapy, showing no organisms, only healthy epithelial cells. No organisms seen, no growth on culture.

side, considerable dysphagia.

Right tonsil enlarged but not inflamed.

General condition poor - ashen colour,
weakness, lassitude.

W.B.C. 2,600 but film revealed many young
polymorphs.

(film - Sp. Vincenti 18/field,
Swab revealed) B. fusiformis 7/field.
(culture - Strep. viridans &
Diplo. catarrhalis
mainly.

(Penicillin Lozenges 2-hourly.
Treatment)
(Pentnucleotide, 3 injections.

9.3.45 (after 24 hours): No dysphagia, inflamma-
tion less, slough separating.

Smear showed no B. fusiformis, and few
Sp. Vincenti (0.7 per field).

10.3.45 (after 48 hours): Symptom-free, general
condition enormously improved, slough now
absent.

Swab: Film - No Vincent's organisms;
Culture - sterile.

12.3.45: Tonsil shows thin transparent film over
deep crater ulcer: W.B.C. 4,000.

20.3.45: Tonsil clean and pink: W.R. + .
W.B.C. 6,800.

Treatment for four days: no relapse in four months.

Comment: The main interest in this case lies in
the fact of a severe Vincent's infection arising
during antiluetic treatment with arsenic and
bismuth, and proving resistant to local chromic
acid therapy, but very rapidly amenable to

Penicillin.

In view of the low W.B.C. count recorded, it is necessary to consider a diagnosis of granulocytopenia, probably as a toxic manifestation of the arsenic therapy, and whether this was in fact, by the consequent lowering of general and local resistance no doubt accentuated by the toxæmia of the abortion, the precipitating factor in the faucial infection.

The steadily worsening condition two days after her abortion and the low and slowly rising W.B.C. count after Pentnucleotide, however, suggest that elimination of these factors, the abortion or the possible agranulocytopenia might not have improved the faucial condition so rapidly as did the Penicillin.

Case 5. Mr J. F., 12 years. Chronic Vincent's Angina of Left Tonsil.

Complaint of slight pain on swallowing for a few days.

Examination: Tonsils moderately enlarged, very septic, with a crater ulcer on posterior aspect of upper pole, left side, filled with slough and localized zone of inflammation around: marked cervical adenitis.

Swab - direct film revealed Vincent's organisms ++: Sp. Vincenti 4.6, B. Fusiformis 3.7 per field.

Treatment: Penicillin Lozenges 2-hourly.

After 48 hours still complains of dysphagia and some adenitis.

Swab: direct film - no Vincent's organisms seen.

After 72 hours: now no pain: crater ulcer clean: no slough nor surrounding inflammation.

After 84 hours: Crater ulcer clean, smooth and healing.
Stopped Penicillin Lozenges.

No recurrence at 5 weeks at which time Tonsillectomy was performed as indicated not so much by the preceding Vincent's Infection as by the general septic condition of the tonsils, undoubtedly a predisposing factor.

Comment: Rapid cure within three and a half days.

Bacteriological cure in 48 hours.

Case 6. L. M., 21 years. Acute Vincent's Angina on Gingivitis.

Complaint of painless bleeding gums for five weeks.

Sore throat for one week, treated with gargles of baking soda, but now still painful on left side.

Examination revealed spongy bleeding gums, especially at lower incisors, with slough in dental sulcus. Pocketing behind lower third molars, especially on right - these were cut only three months ago. Large area of necrotic tissue completely obscuring

the left tonsil: little surrounding inflammation:
 large and very tender upper cervical glands:
 marked foetor: furred tongue. Right tonsil
 septic, otherwise normal. (Plate III)

Swab - direct film revealed Vincent's Organisms
 +++(approximately 40 Spirochaetes and
 40 Fusiforms per field) (Plate V).

Culture gave Strep. pyogenes +, Strep.
viridans +++, Staph. albus (coagulose
 negative) ++.

Treatment: Penicillin Lozenges 2-hourly.

After 48 hours - Symptomatically cured: glands no
 longer tender. Examination showed gums
 clean and firm, left tonsil covered with a
 thin translucent film, with debris only in
 the very depths of the crater ulcer. (Plate IV)

Smear revealed 4 spirochaetes in the whole
 area. (Plate VI)

Culture gave 20 colonies of Strep. viridans
 (600 colonies originally).

Penicillin Lozenges stopped after 80 hours.

After 5 days tonsil clean and healthy, no debris.

Smear showed no Vincent's organisms, no
 growth on culture.

Comment: Immediate relief, symptom-free within

48 hours, cure after 80 hours of therapy. Patient
 stressed the striking relief of pain and foetor
 within a few hours of starting treatment. This
 case again demonstrates the probable dental
 origin in the cutting of 3rd molars.

Three weeks later, the patient complained of painful

gums around the right lower molars.

Examination revealed some debris and inflammation in the pocket behind 8⁷, smear showing a few Vincent's organisms.

Treatment (Penicillin Lozenges 2-hourly for 4 days.
) (Hydrogen peroxide locally applied to the pocket by means of a dressed probe, this to be continued daily for 2 weeks.

Apparently cured in 4 days.

Comment: This dental pocket is obviously the focus of origin, and until it is closed there will always be the risk of recurrence, i.e. predisposing factors must be eliminated before cure can be guaranteed. Penicillin does not easily penetrate into the depths of such pockets unless they are well drained.



Plate III.

Case 6. L.M. Condition when first seen. Large area of necrotic tissue completely obscuring the left tonsil.



Plate IV.

Case 6. L.M. After Penicillin Lozenges for 80 hrs., photograph at 5 days, though clinical condition very little different from that at 48 hrs. Tonsil clean and healthy.

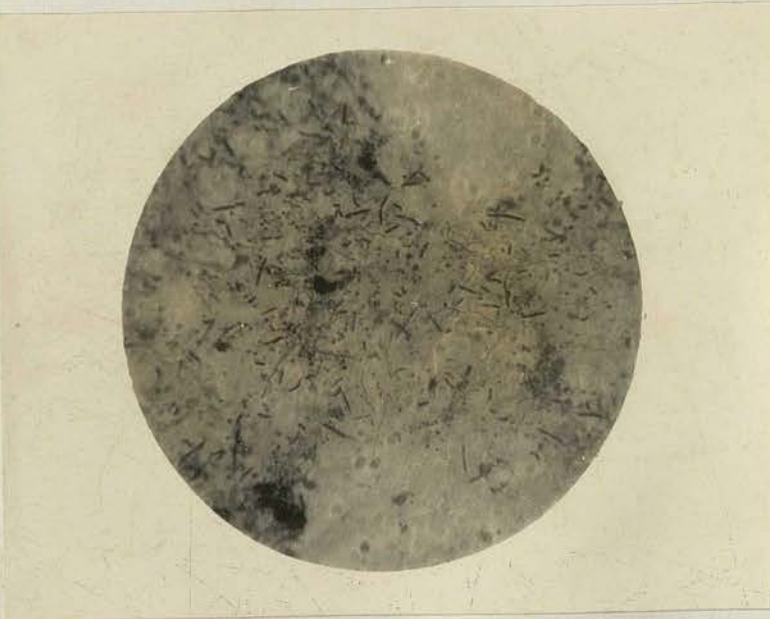


Plate V.

Case 6. L.M. Smear taken when first seen, showing Spirochaeta Vincenti and B. fusiformis in great numbers (about 40/field), also many cocci.

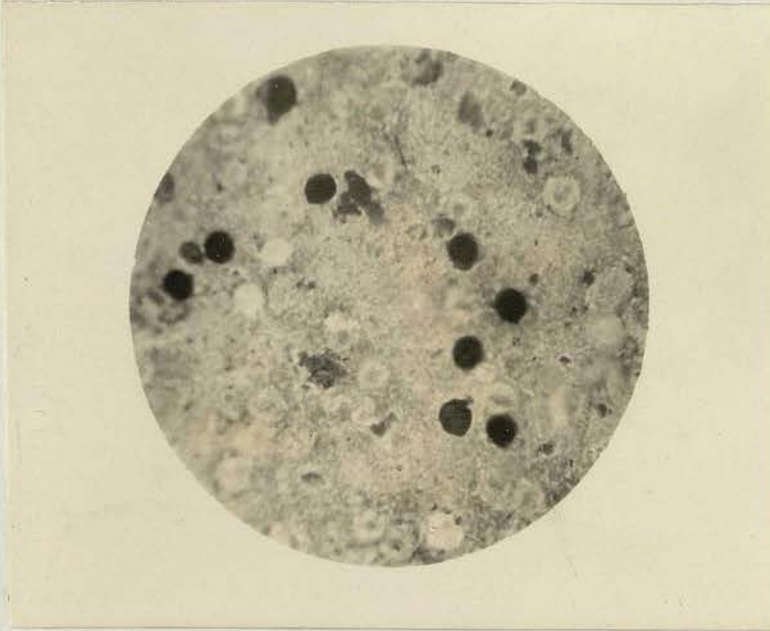


Plate VI.

Case 6. L.M. Smear taken after 48 hrs. therapy, showing epithelial cells and debris with occasional diplostreptococci. B. fusiformis were entirely absent, and Sp. Vincenti very scanty (4 seen in whole area of smear).

Case 7. D.McD. Recurrence of Acute
Vincent's Angina.

History of Vincent's Infection of Right Tonsil two months ago, treated with 20% chromic acid and peroxide painting at least once a day, and peroxide gargles 3-4 times daily over a period of 14 days; associated gingivitis untouched as a hospital in-patient.

Complaint of tender bleeding gums ever since leaving hospital; of sore throat and painful glands for one day.

Examination revealed dirty slough filling crater ulcer of right upper pole, with inflammatory halo; gums inflamed, soft and bleeding easily, with debris in sulcus. Edentulous above except retained root of 14 covered with slough and concealed under dental plate.

Smear revealed Vincent's organisms ++ (Sp. Vincenti 35, and B. fusiformis 17 per field).

Treatment by Penicillin Lozenges 2-hourly.

After 12 hours - complete relief of pain.

After 48 hours - foetor and bad taste gone; no bleeding of gums even after brushing firmly; crater ulcer clean and inflammation absent. Smear showed no organisms.

After 5 days - gums and ulcer clean and healthy: stop treatment.

After 1 month - gums and ulcer still healthy: Tonsillectomy.

Comment: This was a case for whose septic tonsils removal was advised before the onset of Vincent's Infection for which the patient was treated in another hospital. It illustrates well the necessity, if recurrence is to be avoided, of treating the associated gingivitis, the primary source, and of eradicating the predisposing focus, in this case the carious retained root, well concealed. The septic tonsils were obviously a predisposing factor for the spread thereto. This condition proved somewhat resistant even to energetic local treatment, and even after fourteen days of such, soon relapsed.

One of the great advantages of Penicillin therapy is that the substance itself permeates into all sulci and cervices so that there is no necessity for laborious daily painting of the obvious lesions of tonsils and gums as here, treatment being left entirely in the hands of the patient with little or no supervision.

Treatment here was continued for five days to ensure no relapse. Tonsillectomy was indicated by the septic condition on the other side, the crater ulceration on the right having eradicated all obviously septic crypts.

Case 8. R.M.

Subacute Vincent's Angina.

History of Vincent's Infection of tonsils and gums, resistant to local treatment of tonsils with liquor arsenicalis daily for three weeks.

Examination revealed dirty necrotic ulceration of both tonsils and of the gums around certain carious teeth only, especially 123, and large plug of decomposing food in a practically un-cleansable pocket between impacted 4 and 5; erupting 8.

Smear revealed Vincent's organisms + (Sp. Vincenti 0.2, B. fusiformis 8.2/field). Culture gave haemolytic and non-haemolytic streptococci.

Treatment by Penicillin (gelatin) Lozenges every half hour.

After 72 hours - gums clean and pink, slough practically absent from crater ulcer. Smears negative for Vincent's.

After 8 days - gums and tonsils clean and healthy. Penicillin stopped.

Tonsillectomy two weeks later.

Comment: This case well illustrates the predisposing nature of septic tonsils, carious teeth, food stagnation, and erupting molars: also the futility of local arsenic in treatment unless every infective focus is simultaneously swabbed, and the labour involved with little reward, compared with

the self administration of Penicillin to an out-patient.

Treatment gave bacteriological cure in 72 hours, but was continued for eight days.

Case 9. S.D., 24 years. Subacute Vincent's
 Gingivitis.

History of bleeding gums for four months, treated with ascorbic acid and local Gentian Violet, and later by chromic acid and peroxide, with little improvement. No treatment for five days.

Examination revealed ragged, retracted, freely bleeding gums with some debris in sulci and much interdental pocketing: some foetor: teeth blackened by previous medications.

Smear revealed Vincent's organisms + (Sp.
Vincenti 3.2, B. fusiformis 6.6 per field).
Culture gave Strep. viridans.

Treatment by Penicillin Lozenges 2-hourly.

After 24 hours - relief of foetor and bleeding gums,
can now brush them without concern and so aid
the cleansing process.

After 48 hours - symptom-free: gums clean, pink and healthy. Smear negative for Vincent's organisms: no growth on culture.

Treatment until 72 hours.

No relapse in four months.

Comment: A purely gingival infection resistant to "standard" treatments, but responding dramatically

to Penicillin, with cure in 48 hours.

Case 10. D.M., 21 years.
Gingivitis.

Subacute Vincent's

Complaint of painful bleeding gums for four weeks,
with no improvement using glycothymol mouthwash.
Examination revealed spongy bleeding gums with much
debris in the sulci: moderate foetor: tonsils
removed previously.

Smear revealed Vincent's organisms +++ (Sp.
Vincenti 5 and B. fusiformis 38 per field),
with Bacilli predominant.
Culture gave Strep. viridans and Diplococci
catarrhalis ++.

Treatment by Penicillin Lozenges 2-hourly.

After 24 hours - no pain or bleeding, no debris,
clean. Smear showed no spirochaetes but
B. fusiformis 6.4 per field.

After 48 hours - symptom-free, gums normal.
Smear - no Spirocheta Vincenti: B. fusiformis
1.7 per field.
Culture - no growth.

After 72 hours - smear negative.

Treatment continued to total of five days.

No recurrence in five months.

Comment: A purely gingival infection responding
dramatically to Penicillin with cure in 48 hours.
Spirochaetes apparently more susceptible than
fusiforms to Penicillin.

Case 11. E.McC., 21 years. Acute Gingivo-Stomatitis.

Complaint of painful ulceration of tongue for three days.

Examination revealed fleshy tender gums and much debris in the sulci around lower incisors, superficial membranous ulceration of outer gum, and deep pocketing around the crown of a newly erupted last molar with some debris and easily bleeding edges: extensive superficial ulceration of the under-surface of the tongue on both sides, with granular floor, serpiginous margin, and no membrane formation; ulceration most marked on the right, close to a sharp broken tooth: marked foetor, furred tongue, foul taste.

Smear revealed Vincent's organisms ++ (Sp. Vincenti 17.6, B. fusiformis 7.8 per field). Culture gave mainly Strep. viridans.

Treatment by Penicillin Lozenges 2-hourly.

After 24 hours tongue less painful, foetor and taste absent, gums free of debris and membrane, debris still in pocket.

After 48 hours - gums and tongue clean and healing: debris in molar pocket.

After 4 days - symptom-free but smear from pocket still shows Vincent's organisms. Treatment for five days.

No recurrence in three months.

Comment: This case illustrates well the usual

preceding trauma of erupting teeth with mucous membrane flap-formation, and the added complication of a sharp tooth which possibly was the start of the lingual ulceration.

Cured by five days therapy although no negative swab was obtained.

Case 12. E.M. Acute Vincent's on
 Bismuth Stomatitis.

Under treatment in V.D. Department as Tertiary Syphilis with Keratitis, and to date has had a total of 4.02 gm. Arsenic, and 2.7 gm. Bismuth: within the last month has had 0.9 gm. Stabilarosan, and 0.6 gm. Bismuth, intramuscularly, and for the last week Radoxon (Vit. C) Tablets.

Complaint of ulcer inside lower lip ten days ago: since then patchy ulceration spreading round the mouth.

Examination revealed patches of purplish pigmentation at site of original ulcer, and on margin of tongue and posterior half of palate, these now healing: active ulceration with some slough and pigmentation on the buccal mucosa, both sides, contacting very carious molars. Gums show marked bismuth blue-line, and debris in sulcus.

Foetor +.

Smear revealed Vincent's organisms + (Sp. Vincenti 1 and B. fusiformis 5 per field).

Treatment by Penicillin Lozenges 2-hourly.

(Buccal mucosa clean and healing,
After 48 hours) pigmented.
(Gums, slight debris, marked blue-line.

Smear completely clear of Vincent's organisms.

After 96 hours - Buccal mucosa and gums clean and healed.

Stop lozenges.

Comment: This case illustrates well the purely secondary nature of the Vincent's organisms, the prime factors here undoubtedly being the carious teeth and the bismuth stomatitis with pigmentation. Again also we have an example of an acute Vincent's occurring in spite of regular intravenous administration of arsenic.

From these cases (summarised below) it is evident that local Penicillin can give almost immediate relief from pain, foetor, and foul taste, complete freedom from symptoms within two days with bacteriological test of cure, and clinical cure and cessation of treatment in an average of four and a half days (limits 3-8 days).

No recurrences are recorded in periods ranging from one to five months, provided the predisposing

factors are dealt with, e.g. carious teeth extracted, septic tonsils removed. In Case 6 this was neglected, with consequent relapse after three weeks.

TABLE XII.

| No. | Description of Case | Duration of treatment | Duration of Treatment until | | Duration of cure or Consequences |
|---------|---|-----------------------|-----------------------------|--------------|----------------------------------|
| | | | Negative Smear | Symptom-free | |
| 3 | Acute Dental & Buccal | 4 days | 2 days | 2 days | 3 mos. |
| 4 | Acute Faucial | 4 " | 2 " | 2 " | 4 " |
| 5 | Chronic Faucial | 3½ " | 2 " | 3 " | Tonsillectomy at 5 wks. |
| 6 | Acute Dental & Faucial | 3½ " | 3-5 " | 2 " | 5 wks. |
| 7 | Recurrence of Acute Dental & Faucial | 5 " | 2 " | ½ " | Tonsillectomy at 4 wks. |
| 8 | Persistence of Chronic Dental & Faucial | 8 " | 3 " | 3 " | Tonsillectomy at 2 wks. |
| 9 | Subac. Dental | 3 " | 2 " | 2 " | 4 mos. |
| 10 | Subac. Dental | 5 " | 3 " | 2 " | 5 mos. |
| 11 | Acute Dental & Lingual | 5 " | ?5 " | 4 " | 3 mos. |
| 12 | Acute Dental & Buccal on Bismuth | 4 " | 2 " | ½ " | 6 wks. |
| Total | | 45 " | 27 " | 21 " | |
| Average | | 4½ days | 2.7 days | 2.1 days | |

TABLE XIII.

| Case | Approx. numbers per microscopic field (oil immersion) | | | | | |
|------|---|---------------|---------------------|---------------|---------------------|---------------|
| | Original Smear | | Smear after 24 hrs. | | Smear after 48 hrs. | |
| | Sp. Vincenti | B. fusiformis | Sp. Vincenti | B. fusiformis | Sp. Vincenti | B. fusiformis |
| 3 | 50 | 50 | | | - | - |
| 4 | 18 | 7.1 | 0.7 | - | - | - |
| 5 | 4.6 | 3.7 | | | - | - |
| 6 | 40 | 40 | | | 0.04 | - |
| 7 | 35 | 17 | | | - | - |
| 8 | 0.2 | 8.2 | - | 0.8 | - | - |
| 9 | 3.2 | 6.6 | 0.5 | 0.3 | - | - |
| 10 | 5 | 38 | - | 6.4 | - | 1.7 |
| 11 | 17.6 | 7.8 | 0.1 | 0.75 | 2.1 | 2.9 |
| 12 | 1 | 5 | | | - | - |

On tabulating the bacteriological results, it is seen that -

(1) In the original smear:

Sp. Vincenti predominates in 4 of 10 cases,
B. fusiformis " " 4 " 10 "
 Numbers are approx. equal in 2 " 10 " .

(2) In the smear after 24 hours:

Sp. Vincenti is the more resistant to Penicillin in 1 of 5,
B. fusiformis " " " " " " 2 of 5,
 Both are equally resistant in 2 of 5 cases.

(3) In the smear after 48 hours:

Sp. Vincenti is the more resistant to Penicillin
in 1 of 3 cases,
B. fusiformis is the more resistant to Penicillin
in 1 of 3 cases,
Both are equally resistant to Penicillin in 1 of
3 cases.

Although I have specified the one organism as "more resistant" than the other, perusal of the figures makes it evident that it is rather the simple fact that the organism, bacillus or spirochaete, originally present in greater numbers, takes longer to be eliminated than its less numerous associate.

There is thus no appreciable difference in the susceptibility of either organism to Penicillin.

SUMMARY and COMCLUSIONS in CHAPTER III, Para (2).

The aetiology of Vincent's Angina is reviewed with regard to predisposing factors, local and general, with secondary bacterial invasion and the primary focus of gingivitis.

A further theory of virus origin is mentioned.

Diagnosis, clinical and laboratory, is discussed.

Treatment is considered in its varying forms, using arsenicals, oxidising agents, dyes, vitamins, and sulphonamides.

A new treatment, using only Penicillin Lozenges,

is suggested.

Two cases treated by previous methods are mentioned. Ten cases cured by the suggested treatment are described in detail and comments appended.

Penicillin Therapy clearly is a very striking advance in the treatment of infection with Vincent's organisms, whether it be acute or chronic, faucial or dental. Among its advantages are:-

1. Its simplicity, which requires no longer the daily attendance for painting or injections but, once the diagnosis is confirmed, merely the holding of a small lozenge in the mouth for 3-4 days.
2. The absence of disagreeable taste or discomfort of frequent painting. The lozenges have only a slightly bitter taste which may be masked if desired.
3. Its reliability of cure so far as can be judged from the cases seen. The delay in Cases 6, 10 and 11 suggests that very deep pocketing may harbour a residual infection liable to flare up at a later date and which therefore must be cleared up to prevent relapse.
4. Speed of action - bacteriological cure in 48 hours in all cases except 6, 10 and 11, all dental type and with some pocketing. Therapy was

continued for 4-5 days to confirm clinical cure.

5. Success where other methods have failed, well illustrated in Cases 7, 8, 9 and 10, which relapsed after various routine therapies.

Case 4 is of particular interest in that it throws rather a new light on the use of intravenous organic arsenicals in the treatment of Vincent's angina since, if an acute angina can develop while the patient is actually receiving arsenic, little can be said in favour of its use in treatment.

There are of course disadvantages, the greatest of which lies in the necessity for accuracy of diagnosis before commencing treatment for, as already mentioned, there may be a superadded infection with Vincent's organisms on a syphilitic or neoplastic lesion, or masking a diphtheria or agranulocytosis.

CHAPTER III.

Para (3)

ACUTE STREPTOCOCCAL INFECTIONS

including:-

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| Tonsillitis | 89 |
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CHAPTER III.Para (3). ACUTE STREPTOCOCCAL TONSILLITIS.

Acute Tonsillitis due to *B. haemolytic streptococci* (Syn. Strep. pyogenes) is a common condition: its clinical features of sore throat, dysphagia and upper cervical adenitis, with perhaps fever and malaise, are too well known to need description. It is usually regarded as a self-limiting disease lasting five to ten days, unless complicated by peritonsillar abscess, or later by nephritis or rheumatic fever, and as such is left to run its course or is treated by the family physician, so that few cases are seen in hospital practice.

The usual management of simple cases involves bed and isolation, care of the bowels, salicylates to control the temperature and protect the heart and joints, and sulphonamides if the case is severe and shows constitutional upset. Any local treatment is purely palliative, and includes gargles, paints and sprays of oxidising agents or antiseptics, any beneficial action of which is very temporary and unlikely to have much effect on the bacterial content of mouth and throat. Their greatest value, however, lies in their mechanical cleansing action and stimulation of

movement and secretion.

The routine use of sulphonamides in uncomplicated cases has been criticised by many and it has been reported that sulphanilamide did not reduce the severity of symptoms, shorten the period of incapacity or carrier state, nor lessen the incidence of complications (Rhoads and Afremow, 1940), while sulphanilamide and sulphapyridine had no beneficial effect on the course of the infection, even permitting its onset while being administered, and did not influence the carrier state (Hopkins, 1941). There is no doubt, however, that sulphonamides are indicated and will continue to be administered where there are local or general signs of the spread of infection beyond the tonsil.

Other methods of treatment have included the use of bismuth, although its mode of action does not seem to be thoroughly understood. This has been given by intramuscular injection when it is claimed that the pain, temperature and malaise rapidly subside, and the exudate and swelling of the lymph nodes promptly disappear (Monteiro, 1941). Recently the inconvenience and sequelae of intramuscular injections have been rendered quite unnecessary by the administration of the bismuth as its heptadienecarboxylic acid salt

in rectal suppositories, when equal results with the advantages of easy administration and infrequent dosage, absence of toxicity and of sensitisation as with sulphonamides, are claimed (Siber, 1943; Stovin, 1944).

Advances in local therapy have included the use of a lozenge containing sulphanilamide for slow release in the oral cavity (Garson, 1943) by which the period of hospitalisation is said to be reduced from 5.1 days to 2.6 days, and the temperature reduced to normal in 48 hours in 44% of cases, compared with 2% of controls. More recently, a preliminary report on the use of Penicillin Pastilles (MacGregor and Long, 1944) claimed more rapid improvement by the use of these alone, and the clearance of B. haemolytic streptococci from cultures in 48 hours, in 13 out of 17 cases.

In the field of local treatment there arises the question of infectivity by droplet spray, of major importance in cases of hospital sore throat occurring in the wards. It was with this in mind that I determined to investigate further the use of Penicillin locally in the few cases of acute B. haemolytic streptococcal tonsillitis that came under my charge.

In the following cases progress was judged both

clinically, by assessment of symptoms and signs, and bacteriologically by throat swabs taken from the surface of both tonsils once every 24 hours and plated at once on blood agar, incorporating Penicillinase for all swabs from patients who had had Penicillin.

TABLE of CASES.

TABLE XIV.

| No. | Type of Tonsillitis | Duration of Treatment until | | Method of Treatment |
|-----|---------------------------|-----------------------------|----------------|------------------------|
| | | Clinical cure | Negative swabs | |
| 104 | Catarrhal with Pyrexia | 1½ days | 2½ days | Penicillin Lozenges |
| 17 | Follicular | 2 " | 2 " | do. |
| 42 | do. with Pyrexia | 4 " | | do. |
| 105 | do. with Malaise | 3 " | | do. |
| 112 | do. with Pyrexia | 2 " | 2 " | do. plus Sulfa-diazine |
| 41 | do. do. | 5 " | | Sulphathiazole |
| 14 | do. with Oedema & malaise | 7 " | 4 " | Penicillin Lozenges |
| 113 | do. do. do. | 3 " | 3 " | do. plus Sulfa-diazine |

TABLE XV.

| No. | B. Haem. Strep. Colony-count at 24 hr. intervals. | | | | |
|-----|---|-----|-----|-----|-----|
| | Original Habitat | 1 | 2 | 3 | 4 |
| 104 | 400 | 100 | | | |
| 17 | 120 | | | | |
| 42 | 1200 | 200 | 400 | 29 | 120 |
| 105 | 600 | 75 | 28 | | |
| 14 | 1200 | 130 | 35 | | |
| 112 | 230 | 150 | | | |
| 113 | 150 | | | | |
| 41 | 800 | 800 | 800 | 600 | 13 |

It is difficult to draw conclusions from so few cases, but I think the broad principles can be judged by comparison of clinically similar cases.

Take for example Cases 42, 112 and 41, all of whom had bilateral follicular tonsillitis with malaise and pyrexia, and from whom a throat swab gave sheet haemolysis on culture. Treatment with Penicillin Lozenges alone (Case 42) resulted in clinical cure in four days but the throat swab never became entirely negative, and tonsillectomy was performed one week later, when the tonsillar crypts were found to contain many *B. haemolytic streptococci*. In Case 112, however, treatment by Penicillin locally, and sulfa-diazine in full doses orally, resulted in clinical and bacteriological cure within 48 hours. Sulphona-mide therapy alone in Case 41 gave clinical cure only after five days, and even then the throat swab showed a few colonies of *B. haemolytic streptococci* on culture. Case 105 is even more striking in that a similar condition apparently resolved clinically after three days of ambulant treatment with Penicillin Lozenges alone, but bacteriologically the throat was never clear of Haem. Streps. She returned, however, three days later with, this time, marked unilateral follicular infection and in addition oedema and

bulging of the soft palate and some constitutional disturbance (Case 113). On this occasion rest in bed with full doses of sulfadiazine and Penicillin Lozenges locally resulted in complete clinical and bacteriological cure in three days. An identical case (Case 14) treated with Penicillin Lozenges alone dragged on for seven days before clinical recovery, although negative swabs were obtained after four days.

On the other hand, Cases 104 (catarrhal) and 17 (follicular), both early cases, were clinically cured with no signs of faucial inflammation in 36 and 48 hours respectively, and clear swabs obtained then or shortly after, without recurrence.

Considering the bacteriology of these cases (see Table II) as regards the *B. haemolytic streptococcus*, colony counts reveal a striking reduction in the number in the first 24 hours, e.g. Cases 17, 42, 14, 105; and after that a progressive but less marked decrease, suggesting that although the Penicillin could deal with all the superficial or free organisms (and these within an hour or two) it could not prevent the constant inoculation of the faucial field from the depths of the crypts. It is I think significant to note that in Case 41, treated with sulphonamide and local gargles only, the colony-count remained practically unchanged

until four days after the start of treatment.

As previously stated, the only beneficial action of gargles, paints and sprays is by mechanical cleansing, and that is of considerable value. This action too is present in the local Penicillin Therapy for the constant presence of the bitter agar lozenge in the mouth stimulates salivation, Nature's mouthwash, which necessitates frequent swallowing and faucial movement.

Gargles, paints and sprays have been shown to have little or no lasting effect on infectivity by droplet spray which, depending on the form of expulsion, may originate in the front of the mouth or the back of the throat. By local Penicillin therapy, however, the former is rapidly and effectively sterilized, and the latter practically so, an enormous advantage when we have to consider the nursing and isolation of these patients in a large common ward.

We have therefore the broad facts that in acute B. haemolytic streptococcal tonsillitis, the routine treatment, with sulphonamides or bismuth where indicated, will give symptomatic and clinical improvement without regard to the patient's infectivity during treatment or to the consequent carrier state; while Penicillin locally will clear up entirely the early cases (where the organisms are as yet within reach),

and in the later cases will clear up the superficial infection and so control the local infectivity in the majority of cases; but when infection has penetrated into the depths of the tonsillar crypts no local therapy will reach them and their work of necrosis and pus formation will continue unhampered.

Obviously then, the ideal is a combination of the two methods, local and general (when constitutional upset or local signs of spread indicate the use of the latter), whereby we can simultaneously attack the infection (a) from the surface and so eliminate superficial infection and droplet spray, and (b) from the depths by means of blood-borne therapy - a "war on two fronts" as it were.

Cases 112 and 113 were treated thus and show complete cure within three days. In these I used sulfadiazine, but there is no reason to suppose that bismuth or systemic Penicillin would not be as good or better.

The chief indication for Penicillin Lozenges in acute haem. strep. tonsillitis would therefore seem to be as the sole medication for prophylaxis and treatment of early cases, and, in combination with systemic therapy, in cases showing evidence of spread of infection.

A word of warning is necessary, however. Every

medicine has its specific indications and sooner or later Penicillin Lozenges will be released to the public, who expect it as a panacea for all sore throats, but will have to learn, for example, that the doctor and his antitoxin are much to be preferred in diphtheria, which in its early stages is just another sore throat.

In the treatment of cases which have progressed to the stage of Peritonsillar Abscess, local or systemic, Penicillin will never replace surgical drainage of pus under tension. Such cases, however, do not end there, for they are at once candidates for tonsillectomy to ensure that this most painful condition does not recur. Some have performed tonsillectomy at the same time as the abscess is opened, and claim safety, relief of pain and permanent cure in one step (Rao, 1942), but experience here has dictated an interval of 4-6 weeks between the operations, much to the chagrin of the patient who is undoubtedly inconvenienced by two separate periods of hospitalisation. In view of this, the following case is of interest.

The patient, Mrs A., was first seen five days after the incision of her second peritonsillar abscess within a month, when the wound was still open and

oedema of the palate still evident. Treatment was commenced with Penicillin Lozenges and Sulfadiazine in full doses, followed, after 48 hours, by tonsillectomy. Sulfadiazine, 3 gm. per diem, and Penicillin Lozenges were continued after operation. Apart from a slight post-operative rise of temperature (99° F.) she showed no reaction whatsoever and one week later the fossae were healing well with little scarring.

It is difficult to draw conclusions from one case, but at least it suggests that now, when we can control all possible infection, local and general, we can safely advance the date of tonsillectomy to within a day or two of incision of the abscess, thus avoiding the dense scarring so often encountered at the later date, and at the same time the inconvenience of delay to the patient. If this be so, then we have achieved something.

Another case of local Penicillin therapy in operations was that of Mrs S., who had a history of afternoon rises of temperature over eighteen months and on whom Cholecystectomy and Appendicectomy had been performed to eliminate possible septic foci. There was also a history of two attacks of tonsillitis within three weeks.

Penicillin lozenges were administered for two

days before and four days after dissection of tonsils. There was a good deal of after-pain.

Penicillin in this case did not seem to be of marked benefit in local treatment but temperature was below 98.4° F. for the period of fourteen days after operation, for the first time in eighteen months.

Four cases of Group A haemolytic Streptococcal (Syn. Strep. pyogenes) Carriers have so far been treated.

Case 55 (N.H.) had had repeated throat swabs positive for group A. Haem. Streps., but after 48 hours of treatment with Penicillin lozenges swabs were negative, and after four days' treatment continued negative with no relapse in four months, although streptococci doubtfully haemolytic and not yet of group A were found ten days after cessation of treatment.

Case 103 (S.N.H.), a convalescent carrier, showed negative swabs after eight days of lozenge treatment but relapsed within three days.

Case 117 (K.B.M.), a paradoxical carrier who had failed to respond to a previous course of Sulfadiazine, was treated with Penicillin lozenges and Sulfamezathine simultaneously, and gave negative swabs in 48 hours.

Case 126 (N.McK.), who showed positive swabs after treatment of the acute stage with gargles and sulfadiazine, still showed numerous group A. Haem. Streps. after eight days of Penicillin lozenge therapy.

These findings are in agreement with recent work by MacGregor and Long (1944) who found that the majority of carriers relapsed after treatment, but could be kept free so long as they continued to use the Penicillin lozenges.

In a somewhat similar category was Case 36 (T.C.) with a history of evening rises of temperature of unknown aetiology for the previous six months. Clinical examination showed no obvious septic focus though the tonsil-beds were suspect. Throat swab revealed no Strep. pyogenes, but many viridans and a few faecalis streps. Penicillin lozenges were given for six days with elimination of Strep. viridans, while his temperature never rose over 98.6°F. during that period.

Local Penicillin therapy is also indicated in Ulcerative Conditions of Mouth due to Streptococci.

A striking case was F.G. (16), with a history of accident involving loss of teeth from left upper jaw, followed by repeated attacks of streptococcal gingivitis with ulceration severe enough to cause pain and

swelling of the cheek, and constitutional upset with temperature 103°F. These had been treated, over a period of eighteen months, by two full courses of sulphapyridine which relieved the condition for 2-3 weeks, after which it flared up once more, and one of sulphathiazole which failed to give any relief whatsoever. Later, local treatment with arsenicals, silver nitrate, and gentian violet had all proved equally futile.

When first seen there was extensive superficial ulceration of the adjacent surfaces of gum and cheek, the latter markedly granular and easily bleeding. Smear showed no Vincent's organisms and culture yielded slightly haemolytic streptococci. Treatment with Penicillin lozenges was commenced and within 24 hours gave symptomatic relief and no growth on culture from a swab: it was continued for three days, by which time the raw area was perfectly clean and healing well. Convalescence was uninterrupted apart from slight irritation of the area when the dental plate was reinserted. Since then the only trouble has been an infra-orbital neuralgia necessitating nerve section, after which operation Penicillin lozenges were administered as a prophylactic. She has had no recurrence in five months.

SUMMARY and CONCLUSIONS in CHAPTER III, Para (3).Acute Tonsillitis:

The usual therapy involving the use of gargles, paints and sprays is discussed, and also recent advances, including the administration of bismuth intramuscularly and rectally, of sulphonamides and Penicillin locally. Individual cases treated (eight) are stated in tabular form as regards clinical and bacteriological results, and similar cases are compared and contrasted.

From the results it is concluded that local Penicillin therapy will cure early cases, while in later cases it will control the local infectivity but will not prevent extension to peritonsillar abscess formation. In other words local Penicillin treatment is indicated as prophylaxis, in treatment of early cases, and in conjunction with other methods in treatment of later cases. A warning is appended as to the necessity for correct diagnosis before starting treatment.

Peritonsillar Abscess:

Former methods of treatment are outlined and the suggestion made that, being able to control local and general sepsis, tonsillectomy is possible with safety very soon after incision of the abscess.

Post-operative control of a septic tonsillectomy case is also possible.

Carrier-state:

Four cases are treated without marked success. The general finding seems to be that the majority of cases can be kept free only as long as they are taking the lozenges.

Ulcerative Gingivitis (Streptococcal):

One case which had proved resistant to all other methods of treatment was dramatically cured, suggesting that Penicillin is the treatment of choice in such conditions.

SECTION 2.

THE USE OF PENICILLIN SNUFF
IN THE NOSE.

CONTENTS.

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| <u>CHAPTER I</u> describes the choice of a nasal snuff, and its composition and administration with details of the applicators used: Plans are laid | 107 |
| <u>CHAPTER II</u> contains details of the few bacteriologically controlled experiments done | 114 |
| <u>CHAPTER III</u> is a detailed account of an investigation by questionnaire into the treatment of the common cold | 120 |
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CHAPTER I.

EXPERIMENTAL METHODS.

CHAPTER I.EXPERIMENTAL METHODS.(1) THE PENICILLIN SNUFF.

Nasal application of Penicillin may be by insufflation of a powder, or instillation of a solution as drops. For this work I chose the powder, in view of previous experience (unpublished) with sulphonamide snuffs, and of the findings of other workers (Delafield, Straker and Topley, 1941); and because, following the course of the inspired air (Lucas and Douglas, 1934), a powder becomes adherent to the mucous membrane, over the same distribution as inspired organisms, and there slowly dissolves in the mucoid secretion which its presence stimulates and so gives a higher and more lasting concentration than would a spray.

Dilution of the Penicillin powder was indicated owing to its scarcity and cost, and to the fact that the very high dosage involved by the use of neat powder was not thought essential. At first pure glucose was used as a diluent, later to be replaced by powdered plasma. When however the special containers were designed, the plasma was found unsuitable and I reverted to the use of glucose.

The Penicillin powder was supplied in ampoules of 60,000 units in 258 mgm. and this was considered sufficient to treat three cases. For use therefore 0.86 mgm. Penicillin powder were mixed with 2.2 gm. glucose or plasma (the volume of which was considered appropriate): 0.5% menthol crystals were added for their decongestive effect.

As it was essential to avoid introduction of infection, separate containers were supplied to each patient.

(2) APPLICATION OF THE SNUFF.

The first containers used were simply sterile glass bottles fitted with a cork. In use, a little of the powder was tipped into the palm of the hand and a pinch applied with the finger and thumb to each nostril in turn and sniffed up into the nose, this being done every two hours.

Soon, however, it was realised that such application was both clumsy and very liable to introduce further infection. The following applicators were therefore designed.

Type A (see sketch) has the advantage that it can be adjusted to give any required dosage automatically measured each time, but it is less robust than the other type and liable to give

way at the narrow neck.

Type B (see sketch) I designed on the lines of the well-known inhalers on the market to-day. It is much more robust, compact and convenient to use, but the dosage applied depends entirely on the patient's powers of inspiration.

Using these applicators it was found that a very fine freely-running powder was essential and as plasma was rather hygroscopic, and menthol oily, both were discarded and recourse had to pure glucose as a diluent. I tried using Benzedrine as a vaso-constrictor in a few cases without marked beneficial effect, and in the end, it was decided, as with the lozenges, that the fewer materials used the less likelihood was there of side-actions or inhibition of the Penicillin. The prescription therefore adopted was -

R_x Penicillin pulv. gr. 0.86
Glucose pulv. ad. gr. 20

and the powder stored in the refrigerator to maintain activity of the Penicillin.

(3) BACTERIOLOGICAL METHODS:

These were the same as described in Chapter I.

(4) CLINICAL METHODS:

Owing to lack of opportunity, very little

bacteriological study was done and, apart from a few cases, results are judged purely on clinical grounds.

(5) SCHEME OF INVESTIGATION:

By far the commonest infective nasal condition met with is the common cold in its various stages. Popular and scientific remedies are innumerable and legion, their very number implying lack of success. I decided therefore to investigate the use of Penicillin snuff in the treatment of the Common Cold by clinical observations and later by bacteriological studies if the opportunity arose.

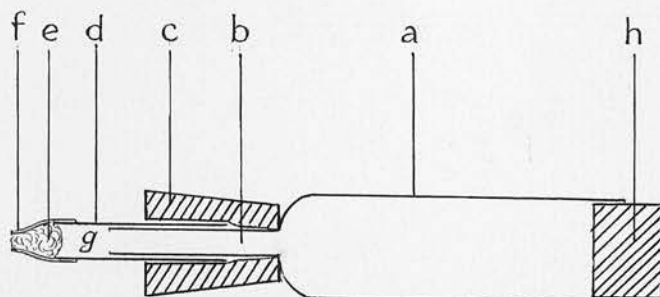


Fig. 1 (actual size).

Applicator A consists of a holding chamber (a) for several days' supply of snuff, with a narrow tubular extension (b) which acts as a fine slow pourer. This fits closely inside the glass tube (d) which bears on its distal end a short length of rubber tubing (f) holding a small wad of cotton wool (e): the proximal end fits into a rubber cork (c) of suitable size to fit into the nostril, and which at the same time lightly grips the tube (b).

There is thus a measuring chamber (g) between the wool-plug (e) and the end of the inner tube (b), the length of which can be varied at will by sliding tube (d) in or out of the rubber cork.

In use, the applicator is held vertically with chamber (a) uppermost, when the snuff runs through tube (b) and fills the measuring chamber (g), the corked end of chamber (a) being tapped gently with the finger if necessary. Then, in the horizontal position, tube (b) is withdrawn from the cork, leaving the measured amount of snuff in tube (d).

The cork is then inserted into one nostril and with the other closed with the finger the patient sniffs sharply, when the inrush of air through the wool-plug (e) carries the snuff well up into the nasal cavity. The process is repeated on the other nostril.

After use the applicator can be washed, sterilised in the autoclave, and a fresh sterile wool-plug inserted. It is refilled by removing cork (h).

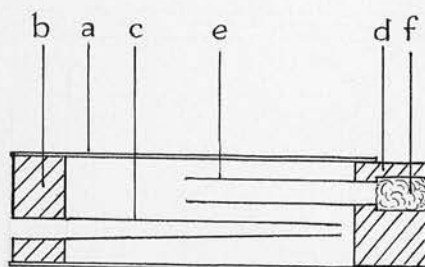


Fig. 2 (actual size).

Applicator B consists of a cylindrical glass chamber (a) closed at one end by a cork (b) fitting flush with the glass end, and carrying a tapered glass tube (c) set eccentrically. The other end is closed by a cork (d) carrying a straight glass tube (e), eccentric, and only partly sunk into it, the rest of the boring being filled with a wool-plug (f).

The applicator is filled by removing cork (d).

In use, the end carrying cork (b) is fitted into one nostril and the patient inhales through that nostril, when air sucked in through the wool-plug (f), traverses the main chamber (a) and carries a quantity of snuff up tube (c) into the nose.

Tube (c) is tapered so as to reduce the intake of snuff and the spillage, the smaller the bore the less snuff escapes.

CHAPTER II.

CLINICAL EXPERIMENTS.

CHAPTER II.CLINICAL EXPERIMENTS.

There was unfortunately no opportunity for bacteriological study of the cases cited in Chapter III to follow. Nor was there much time for experimental work on the lines of Section 1. However, such work as was done is I think worthy of record.

EXPERIMENT I.

- Object: Has Penicillin Snuff any effect on the bacterial flora of the normal nose, and if so how many applications are required?
- Subjects: Post-operative mastoidectomy cases confined to bed.
- Method: Three such patients were chosen and separate swabs taken from right and left nasal cavities. Nasal snuff was then administered and repeated at intervals of 4, 4, 4, and 12 hours, further swabs being taken before each application and at 12 hours after the last. Two received Penicillin snuff and the third coloured glucose.

Results: See Table XVI.

From the Table it can be seen that, omitting Staph. albus (coagulase negative), probably contamination from the skin of the anterior nares not being treated with Penicillin,

Diplo. catarrhalis was eliminated at least after two applications (7 hrs.) if not after one, in all the four sides recorded.

Strep. viridans was eliminated after three applications on one side and two applications on the other side of the nose harbouring it.

Conclusion: The bacterial flora of the normal nose is susceptible to Penicillin snuff, at most three applications (11 hrs.) being required.

TABLE XVI.

| Time Intervals | Organisms - number of colonies before and after Penicillin Snuff. | | | | | | | | | | | | | |
|-------------------------------|---|----------|----------|----------|--------------------|----------|----------|----------|-------------------------------|----------|----------|----------|----------|----------|
| | Strep. viridans | | | | Diplo. catarrhalis | | | | Staph. albus (Coagulose neg.) | | | | | |
| | Case 109 | Case 110 | Case 111 | Case 109 | Case 110 | Case 111 | Case 109 | Case 110 | Case 109 | Case 110 | Case 111 | Case 109 | Case 110 | Case 111 |
| | L | R | L | R | L | R | L | R | L | R | L | L | R | R |
| Before Snuff | 100 | 10 | | | | | | | 15 | 6 | (13) | | | 20 |
| 3 hrs. after 1st | omitted | | | | | | | | 7 | 20 | (11) | | | (2) |
| 4 hrs. " 2nd | 16 | | | | | | | | (1) | (12) | (12) | | | (3) |
| 4 hrs. " 3rd | | | | | | | | | 100 | 200 | | | | |
| 12 hrs. " 4th | | | | | | | | | 8 | 5 | 100 | | | 30 |
| 24 hrs. " 4th | | | | | | | | | 7 | 10 | 2 | | | |
| No. of snuffs to eliminate | 3 | ?2 | | | ?2 | ?2 | 1 | 1 | | | | | | |

EXPERIMENT II.

- Object: Has Penicillin snuff any antibacterial effect in the treatment of the common cold?
- Subject: Patient with a history of five days of nasal obstruction and discharge now purulent.
- Method: Nasal swabs taken from right and left sides. Penicillin snuff applied every two hours for five days. Nasal swabs taken daily.
- Result: See Table XVII.

Thus Pneumococcus and Diplo. catarrhalis are eliminated within the first 24 hours of treatment and remain absent during treatment.

Conclusion is impossible from one case, but the result is striking enough to suggest that any susceptible organism will be similarly eliminated.

TABLE XVII.

| Time Intervals | Organisms - colony counts before/after snuff | | | | | |
|----------------------------|--|-------|--------------------|-------|--------------|-------|
| | Pneumococcus | | Diplo. catarrhalis | | Staph. albus | |
| | Left | Right | Left | Right | Left | Right |
| Original swab | 40 | 600 | 8 | 120 | | |
| After 24 hrs. | | | | | 4 | 50 |
| 48 hrs. | | | | | 5 | 150 |
| 72 hrs. | | | | | 2 | 70 |
| 96 hrs. | | | | | (2) | (4) |
| Eliminated within 24 hours | | | 24 hours | | | |

CHAPTER III.

CLINICAL TRIALS IN THE COMMON COLD.

CHAPTER III.CLINICAL TRIALS IN THE COMMON COLD.

The common cold is regarded as primarily a virus infection of the nose and nasopharynx. This virus, by its invasion predisposes the nasal mucosa to secondary infection by the common pathogens, e.g. Pneumococcus, Staph. aureus, Streptococci, etc., to which are due the sequelae which are the major factor in the symptomatology and duration of the illness - the purulent discharge, the spread of suppuration to the sinuses and perhaps beyond, the descent to the rest of the respiratory tract, and the toxaemia.

If it is possible to control or prevent this secondary invasion, then 'the cold' should be limited to a simple catarrh of very short duration.

The following investigations on the treatment of the common cold concerned the hospital nursing staff, who were requested to report to the Sick Room as soon as they thought they were starting a head cold.

As clinical examination and bacteriological control of these patients was not feasible, the investigation was carried out by means of a questionnaire, a specimen of which is given overleaf. Nurses were examined by the Sister in charge and, if suitable for

Please answer on your fourth day.

1. Is your cold any better ?

2. Describe any nasal discharge now { Amount
Consistence
Colour

3. Has this treatment helped you { more
more quickly } than other methods ?

4. Do you wish to continue this treatment ?

State reasons

.....
.....

Any comments

.....
.....
.....
.....
.....

THE ROYAL INFIRMARY OF EDINBURGHOUT-PATIENT

WARDS 39 AND 40,
ROYAL INFIRMARY,
EDINBURGH 3.

CASE..... Bottle No..... Date.....

Time

NAME

Please answer now :—

1. When and what was your first symptom ?.....

.....

2. Do you suffer from frequent colds ? How often ?.....

.....

3. Is this attack worse than previous ones ?.....

| | | |
|---------------------------------|---|------------------|
| 4. Describe any nasal discharge | { | Amount |
| | | Consistence..... |
| | | Colour |

Report again on your fourth day, and fill in other side.

treatment, filled up page one of the form and received their Penicillin which they used as out-patients for the next four days. They then returned to complete page two, being permitted to continue treatment longer if necessary.

From perusal of the questionnaire it was hoped to judge the type and severity of the cold, its stage when starting treatment, and the presence or absence of secondary infection; later, the effect, if any, of the snuff, subjectively and objectively.

There are two Series of cases.

In Series I three medications were used for the purposes of comparison, viz: (A) 'Sulfex', a suspension of Microform Sulfathiazole in Paredrine: (B) Penicillin Snuff in Glucose or Plasma: and (C) Menthol $\frac{1}{2}\%$ in Glucose or Plasma - the control cases.

Patients were treated in rotation by one of these methods, while ignorant of the exact medication they received.

The results are summarised in Table XVIII.

After some time it was decided to abandon the use of 'Sulfex', so that Series II consists of a comparison of nasal snuffs medicated (Penicillin) and Control (plain glucose and menthol).

TABLE XVIII.
SERIES I - A (Sulfex).

| Case | Stage at start | Progress | Stage at 4th day | Result |
|------|------------------------|---|------------------|--|
| 1 | 2 ^y 36 hrs. | Airway improved, discharge less; other side clear | 2 ^y | Improved |
| 4 | 1 ^y ? | Discharge never became purulent: cleared. | Convalescent | Prevention of 2 ^y infection |
| 10 | 1 ^y 12 hrs. | Cold progressed as usual | 2 ^y | Usual course |
| 12 | 1 ^y 10 hrs. | Airway cleared, no usual downward spread, but discharge became purulent | 2 ^y | Improved slightly |
| 17 | 1 ^y 14 hrs. | Discharge reduced and never purulent | Convalescent | Prevention of 2 ^y infection |
| 20 | 2 ^y 24 hrs. | Temporary clearance only: chronic sinusitis | 2 ^y | Unchanged |
| 21 | 1 ^y 1 hr. | Discharge appeared and became purulent | 2 ^y | Usual course |
| 24 | 1 ^y 20 hrs. | Profuse mucoid discharge eliminated | Convalescent | Prevention of 2 ^y infection |
| 27 | 2 ^y 24 hrs. | Improved but not cured: purulent discharge reduced to mucoid | Convalescent | Improved |
| 7 | 1 ^y 2 hrs. | Unpleasant reaction dictated cessation of treatment | 2 ^y | Reaction |

TABLE XIX.
 SERIES I & II - C (Control).

| Case | Stage at start | Progress | Stage at 4th day | Result |
|------|------------------------|--|------------------|-------------------|
| 3 | 2 ^y 12 hrs. | Cold progressed, discharge no better Discharge less but not cleared Symptomatic cure in 24 hrs.! Discharge thinner but no more rapidly than usual | 2 ^y | Worsened |
| 9 | 2 ^y 5 days | | 2 ^y | Improved slightly |
| 16 | 1 ^y 12 hrs. | | Cured | Cured |
| 19 | 2 ^y 24 hrs. | | Convalescent | Usual course |
| 23 | 1 ^y ? | Less discharge but now purulent Condition unchanged Less discharge but still purulent Worse at first then clear, but no more rapidly | 2 ^y | Usual course |
| 26 | 2 ^y 3 wks. | | 2 ^y | Unchanged |
| 31 | 2 ^y 1 wk. | | 2 ^y | Improved slightly |
| 32 | 2 ^y ? | | Convalescent | Usual course |
| 54 | 2 ^y ? | Thick green mucoid discharge unchanged Discharge became purulent: transitory help only | 2 ^y | Unchanged |
| 34 | 1 ^y 36 hrs. | | 2 ^y | Usual course |

TABLE XX.

SERIES I & II - B (Penicillin).

| Case | Stage at start | Progress | Stage at 4th day | Result |
|------|------------------------|--|------------------|--|
| 2 | 1 ^y 72 hrs. | Discharge less and never purulent | Convalescent | Prevention of 2 ^y infection |
| 5 | 2 ^y 5 days | Discharge first increased, then eliminated | Cured | Cured |
| 8 | 2 ^y 48 hrs. | Discharge became clear then eliminated | Cured | Cured |
| 13 | 2 ^y 48 hrs. | Purulent discharge less, symptomatic cure | Convalescent | Improved |
| 15 | 1 ^y ? | Discharge never purulent: malaise persisted at first but then symptomatic cure | Convalescent | Prevention of 2 ^y infection |
| 18 | 1 ^y 10 hrs. | Discharge never purulent but persisted mucoid | Convalescent | Prevention of 2 ^y infection |
| 22 | 2 ^y 18 hrs. | Discharge reduced but still purulent: irritant | 2 ^y | Improved slightly |
| 25 | 2 ^y 18 hrs. | Purulent discharge cleared: symptomatic cure | Cured | Cured |
| 52 | 1 ^y 24 hrs. | Dry irritated nose normal in 24-36 hrs. Sulfadiazine used to counter malaise | Cured | Cured |
| 53 | 1 ^y 7 hrs. | Slight watery discharge & irritation cleared | Cured | Cured |
| 55 | 2 ^y 4 days | Profuse purulent discharge clear in 2 days | Cured | Cured |
| 11 | 1 ^y 48 hrs. | Had laryngitis at start and gave up treatment after 2 days as it did not improve | - | Nil |
| 29/ | | | | |

TABLE XX (Contd.)

| Case | Stage at start | Progress | Stage at 4th day | Result |
|------|------------------------|--|------------------|--|
| 29 | 2 ^y 3 days | Nasal obstruction and could not inhale snuff | 2 ^y | Unchanged |
| 33 | 2 ^y ? | Discharge less after 24 hours and never purulent | Cured | Cured |
| 35 | 1 ^y ? | Discharge never purulent as usual: more rapid relief | Convalescent | Prevention of 2 ^y infection |
| 36 | 2 ^y 3 days | Very rapid clearance of the head | Cured | Cured |
| 38 | 1 ^y 24 hrs. | More rapid relief than usual, never purulent | Convalescent | Prevention of 2 ^y infection |
| 39 | 1 ^y 36 hrs. | Discharge eliminated and more rapidly cleared | Cured | Cured |

Consider the cases seen in the early stages, before the onset of secondary infection.

(a) Using preparation 'A' (Sulfex), of seven cases -

3 cases never became secondarily infected;

3 cases ran their usual course or reported only slight improvement;

1 case had an unpleasant reaction and discontinued.

(b) Using preparation C (Control), of three cases -

2 cases ran their usual course with secondary infection;

1 case reported symptomatic cure in 24 hours, a somewhat suspicious finding.

(c) Using preparation B (Penicillin), of nine cases -

8 cases never became secondarily infected;

1 case had laryngitis at the start and gave up treatment after two days.

From these results it can be seen that local Penicillin snuff will effectively prevent the secondary invasion of pyogenic organisms (all of 8 suitable cases), which normally occurs and is controlled by local sulphathiazole in only half the number of cases.

Consider cases which were already secondarily infected at the start of treatment -

(a) Using preparation A ('Sulfex'), of three cases treated -

2 cases were improved by reduction of discharge and increased airway, but not completely cured within the four days;

1 case (a chronic) was unchanged.

(b) Using preparation C (Control), of seven cases treated -

2 cases ran their usual course to natural cure;

2 cases were slightly improved by lessened discharge;

2 cases showed no change in their condition;

1 case progressed in spite of treatment and seemed worse on the fourth day than at the start.

(c) Using preparation B (Penicillin), of nine cases treated -

6 cases reported complete cure and elimination of discharge within four days;

2 cases were improved by reduction of discharge, but not cured;

1 case found inhalation impossible through nasal obstruction.

Thus local Penicillin snuff in about two-thirds of cases will effectively clear up and eliminate the secondary purulent discharge which was only reduced by local sulphathiazole (2 of 3 cases) and unchanged by menthol (5 of 7 cases).

Several of the cases receiving Penicillin snuff are worthy of detailed description.

Case 53 gave a history of seven hours previously

an onset marked by a prickling sensation at the back of the nose, sneezing and a heaviness of the eyes, with a little thin watery discharge. Report on the fourth day claimed complete relief, with no discharge.

Case 15 gave a history of onset marked by sneezing and tickling at the back of the nose with profuse clear watery nasal discharge. Four days later she reported complete relief by the third day, with very little normal discharge, and volunteered the information that the discharge had never become thick and yellow as it did normally during her colds.

Case 52 involved combination of local treatment with the use of systemic sulphonamide. The onset was typical - sense of chill followed the next morning by shivering, a prickling sensation of soft palate and the back of the nose and increasing discomfort and a previous history of such an onset usually followed by nasopharyngeal infection and sinus catarrh, sometimes by descending laryngeal infection. Treatment started twenty-four hours after the first symptoms. In this case local Penicillin snuff was combined with Sulfadiazine, which latter on previous occasions had relieved the symptoms of malaise and sense of chill but never the local symptoms which invariably ran their course, though improved by a day or two in bed.

The result was complete cure without nasal discharge in 24-36 hours.

Case 29 is the only one which does not show improvement under treatment with Penicillin. The explanation, however, is not difficult to find, for the patient volunteered the information that so complete was the nasal obstruction that inhalation of snuff was physically impossible. In such cases it is therefore essential to provide an airway by the use of 2% Ephedrine - saline drops or of a Menthol Inhalation immediately prior to the applications of snuff as often as required.

SUMMARY and CONCLUSIONS.

The bacterial flora of the normal nose is rapidly susceptible to Penicillin snuff. Secondary invaders in cases of common cold can be eliminated by Penicillin snuff.

Clinical review of 38 cases of common cold, of which 18 were treated with Penicillin snuff, shows that such treatment is a distinct advance in that it will in the early stages effectively prevent the secondary invasion of pyogenic organisms, while once that invasion has taken place it will in two-thirds of cases eliminate it within four days.

Penicillin snuff alone may not be adequate and may usefully be combined with decongestants, such as ephedrine or menthol if necessary, and in severe cases with sulphonamides.

SECTION 3.

THE USE OF PENICILLIN IN
INFECTIONS OF PARANASAL SINUSES.

CONTENTS.

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| <u>CHAPTER II</u> details the methods of administra- tion of the Penicillin, the surgery performed and the laboratory methods .. | 138 |
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CHAPTER I.

A REVIEW OF SINUS INFECTION
AND ITS TREATMENT.

CHAPTER I.A REVIEW OF SINUS INFECTION AND ITS TREATMENT.

Infections of the Paranasal Sinuses may be catarrhal or suppurative, the latter being acute, even fulminating, and endangering life, or chronic and indolent.

It is with the acute suppurative infections I propose to deal mainly. These may be simple at first, but if untreated will rapidly become complicated. Probably the first complication in any case is erosion of the bony cortex and infection of the diploe - osteomyelitis. The dangers of such infection lie in intracranial involvement and blood-stream infection.

Extension of infection into the cranium may occur through venous channels or by direct extension through bone, the latter being the route taken in 59.9% cases. It may produce Brain Abscess (33%), Leptomeningitis (32%) or Cavernous Sinus Thrombosis (11%), the responsible air cavity being in 61% of cases the Frontal, and the Sphenoidal in the majority of cases with thrombosis (Turner and Reynolds, 1931).

Treatment of such an acute suppurative sinusitis has always been by surgical drainage of the infected cavity, by the intranasal route first or in the very

early cases, and by the external or radical operation in later or complicated cases. This latter involved wide exposure of bone, especially if osteomyelitis was already present at the time of operation. Statistics have since then shown that osteomyelitis was more common as a post-operative than as a spontaneous complication, being the main factor in the high incidence of post-operative fatalities, the mortality in severe cases of osteomyelitis of the skull being even 80%. The very "life-saving" operation was then liable to be the cause of death.

With the advent of the sulphonamides there came the possibility of controlling the spontaneous complications such as Abscess, Meningitis or Sinus Thrombosis (since the common causal organisms - Strep. pyogenes, Pneumococcus, and much less so Staph. aureus - were susceptible to their action) while surgical drainage released the pus under tension in the sinus and beyond. The incidence and mortality of osteomyelitis, spontaneous or post-operative, remained high however, in part because the common agent, Staph. aureus, was unaffected by the great majority of sulphonamides.

Recently, however, the discovery of Penicillin has given us fresh hope. It provides the only effective treatment, with surgical drainage where necessary, for

acute osteomyelitis, and alone it will hold the infection in check until adequate surgery can be safely performed. Cases have been reported in which surgery and sulphonamides had failed but Penicillin, and later surgery to remove all necrotic bone, was an unqualified success.

Chronic Sinus Infection is a very different problem. There the causal organisms are buried in the depths of redundant, granulating, unhealthy epithelium, a source of constant toxic absorption.

Surgical removal of every vestige of this now non-functioning mucous membrane, with ingrowth of a healthy lining, has previously given very good results. Sulphonamides, and now Penicillin in its turn, have been suggested as suitable agents for dealing with this infection by conservative means. As the infection is of low grade, and confined to the bounds of the air-cavity, local application is indicated. Neither agent however has given much promise of success.

For discussion of the use of Penicillin see "Conclusions".

CHAPTER II.

CLINICAL METHODS.

CHAPTER II.CLINICAL METHODS.

All the cases described were admitted to the wards as surgical emergencies.

Penicillin, as a solution of 1,000 units per cubic centimetre, was administered, if at all, both systemically as a continuous intramuscular drip at the rate of 100,000 units per 24 hours, and locally by injection through narrow-bore rubber tubes inserted into the air and abscess cavities at the time of operation, and stitched in position.

Surgery consisted of the minimum required to ensure drainage of the pus - intranasal turbinotomy, antrostomy, ethmoid curettage, or frontal probing; and extranasal only in later or complicated cases and again restricted to simple opening of orbital or frontal abscess, or of the floor of frontal sinus, and introduction of tubes for local administration of Penicillin. Dry dressings were then applied and the wounds undisturbed until removal of stitches or tubes.

Specimens of pus were taken at operation, and the organisms cultured and identified as described in Section I, Chapter I. Consecutive daily specimens were taken until the discharges became and remained

sterile, when the Penicillin administration could be discontinued.

Detailed case histories and conclusions follow.

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CHAPTER III.

CLINICAL TRIALS AND RESULTS.

CHAPTER III.CLINICAL TRIALS and RESULTS.

Case 1. E.C., 46 years. Acute Spheno-Ethmoidal Sinusitis: Drainage and Sulphonamides.

History of Influenza followed by Acute Frontal

Sinusitis (right) for three weeks, treated by inhalations and drops.

Examination: slight oedema over right eye, tenderness of floor and anterior wall of right frontal sinus: no antral or ethmoidal signs. Fauces reddened and swollen: no view of nasopharynx though slight mucopus was seen on posterior pharyngeal wall.

Slight nuchal tenderness and limitation of movement.

Temperature 100.6° F., Pulse 88.

X-ray revealed opacity of right sphenoidal and posterior ethmoidal sinuses.

Treatment by Sulphapyridine in full doses.
Inhalations, nose drops^o and head-light baths.

Day 2: Definite neck rigidity with Kernig's sign weakly positive: temperature increased: thick pus seen in nasopharynx.

Lumbar C.S.F. showed increased pressure with 1500 cells/c.mm. Gram positive cocci in films but no growth on culture.

ø Of Ephedrine 2% in saline.

Day 3. **Exploratory** operation under general anaesthesia. Right antrum, anterior ethmoid and frontal sinus clear. Pus under pressure in sphenoidal and posterior ethmoidal cells - these were opened up for free drainage.

Lumbar C.S.F. showed increased pressure, 4,000 cells/c.mm., Staph. aureus on culture.

Treatment - Sulphapyridine replaced by Sulfadiazine.

Day 5. Comatose.

Day 6. Death. Post-mortem examination revealed extradural abscess over sphenoidal-ethmoidal area tracking to meninges and cerebellar cortex.

Case Summary:

Case of Acute Spheno-Ethmoidal Sinusitis, admitted before Penicillin became available in the hospital.

On admission there was evidence of meningeal involvement, and Sulphapyridine, then our 'routine' sulphonamide, was administered and conservative treatment instituted. Frank meningitis however developed, in view of which surgical drainage was performed: and as Staph. aureus was found on culture, Sulfadiazine given. In spite of this, however, the patient went rapidly downhill, and died of Staphylococcal Meningitis.

Case 2. A.C., 16 years. Early Acute Ethmoiditis
- Drainage and Sulphonamides.

History of sore throat for four days followed by flare-up with temperature 103°F. and oedema of left eye, treated with 2.5 gm. Sulphonamide, after which temperature was normal but oedema increased and was accompanied by tenderness over upper inner canthus - thus for four days.

Examination: Left eye proptosed, movements normal, oedema of lids. Tonsils inflamed: left middle turbinate swollen. Ethmoidal tenderness. Temperature 98.4°F., Pulse 56.

X-ray: opacity of left ethmoidal area.

Treatment: Sulfadiazine in full doses.
Hot fomentations.

Day 2. Oedema and tenderness less: temperature normal.

Intranasal drainage operation under general anaesthesia. Curettage of anterior ethmoidal cells released pus: intranasal antrostomy (left) to release mucoid material.

Swab - culture revealed Staph. aureus.

Sulfadiazine continued.

Day 10. Discharged.

Case Summary:

A case of acute ethmoiditis with oedema of orbital tissues, due to infection with staph. aureus, which responded to simple drainage and administration of sulfadiazine.

Case 3. J.W., 14 years. Acute Fronto-Ethmoidal Sinusitis with Orbital Abscess - Sulphonamides and Penicillin.

History of severe frontal headache and vomiting for four days, with pain over the left eye.

Examination: Left eye completely closed by oedema: marked tenderness over the left frontal sinus: oedematous left middle turbinate, but no pus seen. Nose and throat otherwise normal. Temperature 101.6°F., Pulse 120. X-ray - opacity of ethmoidal cells, and clouding of left frontal sinus.

Treatment by Sulfadiazine in full doses.
Hot fomentations.
Cocaine probes in middle meatus.

Day 2. Increased oedema over left frontal area with increased tenderness and temperature. Probably Osteomyelitis. Drainage operation under general anaesthesia. Anterior ends of left middle and inferior turbinates removed: ethmoidal cells curetted, releasing much pus: frontal and maxillary sinuses drained intranasally. Cultures yielded Staph. aureus. Sulfadiazine continued.

Day 3. Still much oedema and tenderness. Temperature subsiding. W.B.C. 15,400.

External ethmoidal sinus Operation under general anaesthesia, revealing left orbital abscess, and limited drainage of frontal sinus. Drainage tubes inserted into orbit and frontal sinus.

Day 4. Still much oedema, now spreading over eyelids and face. Temperature normal, Pulse 84.

Treatment - Stop sulfadiazine at total of 18.5 gm.

Start Penicillin: I.M. Drip - 90,000 units per 24 hours.

Locally - 10,000 units as twice daily injections via drainage tubes.

Day 5. Oedema and tenderness subsiding. Temperature normal.

Day 6. W.B.C. 10,000. Specimens from frontal sinus and orbit showed Staph. aureus ++ in both.

Day 8. Specimens showed Frontal ++, Orbital 1 of Staph. Aureus.

Day 9. Specimens showed Frontal V.F., orbital - Staph. aureus.

W.B.C. 11,250. Oedema and tenderness much less. Orbital drain removed, further Penicillin to be administered by wide-bore needle.

Frontal drain retained.

Penicillin I.M. Drip stopped - 450,000 units given (total).

Day 13. Now only slight oedema of eyelids: no tenderness. Frontal drain removed, further Penicillin (local) to be administered by wide-bore needle.

Day 15. Penicillin (local) stopped: 110,000 units given (total).

Day 19. Wound healed.

Day 27. W.B.C. 5,900.

Day 31. Patient discharged but will report every two weeks.

Convalescence uninterrupted.

Case Summary:

Case of Acute Fronto-Ethmoidal Sinusitis with Orbital Abscess due to Staph. aureus infection which was treated first by Sulfadiazine and conservation; but the onset of probable Frontal Osteomyelitis demanded operative drainage as well. After three days treatment the condition remained uncontrolled and Penicillin therapy was commenced, resulting in virtual clinical and bacteriological cure within five days (560,000 units Penicillin).

Case 4. T.S., age 17 years. Acute Frontal Sinusitis with Osteomyelitis and Orbital Abscess.

History of oedema of right eyelids for three days: prominent painful right eye for one day.

Examination. Right eye closed by oedema of lids, spreading over frontal area, and of the conjunctiva: proptosis and considerable limitation of

all movements of the globe; light reflex normal. Fundus oculi showed dilated veins but no pappilloedema. Tenderness of all orbital margins. Temperature 100.4°F., Pulse 64. X-ray - opacity of right frontal and both maxillary sinuses.

Treatment: (1) Drainage operation under general anaesthetic. Limited external drainage of frontal sinus and orbital abscess releasing thick foul pus, culture of which gave non-haemolytic streptococcus (orbit) and diphtheroids with Morax diplo-bacillus (nose): drainage tubes inserted.

Removal of anterior end of right middle turbinate, and fronto-nasal duct probed.

Double Intranasal Antrostomy.

(2) Penicillin - I.M. Drip, 100,000 units per 24 hours;
Locally - 40,000 units per 24 hours in 40 cc., given as 2-hourly injections through drainage tubes.

Day 3. Fistula has formed from orbital abscess through upper inner canthus. Drainage tube inserted permitted wash-through of abscess. Oedema of frontal area increased.

Day 4. Subperiosteal Frontal Abscess incised and drained through very small incision at hair margin.

Hot fomentations. Pus contained anaerobic streptococci and leptothrix. Pus from orbit and frontal sinus proved sterile on culture.

Day 7. Orbital drainage and frontal sinus drainage tubes out and wound lightly packed with dry gauze. Total - 240,000 units locally.

Frontal abscess - tube inserted for wash-out and local Penicillin. Pus still contains anaerobic streptococci and leptothrix.

Day 9. Pus from frontal abscess now contains only very few anaerobic streptococci.

Day 11. Stop Penicillin - I.M. drip, total
1,000,000 units;
local, total 160,000
units;
so that total local = 400,000 units.

Day 22. Patient discharged: will report at intervals.

Day 32. Orbital wound discharging: pus in both sides of nose. Treated by hot fomentations and nasal douching.

Day 36. Wound has stopped discharging.

Day 53. Mass of granulations around medial end of wound: bluestoned.

Day 114. Still small fistula at medial end, leading into the frontal cavity: fronto-nasal duct widely patent.

Day 125. Wound healed.

Case Summary:

Case of Acute Frontal Sinusitis with Osteomyelitis and Orbital Abscess treated by intranasal and limited extranasal drainage and Penicillin for ten days (1,400,000 units) with recovery though partial relapse three weeks later.

Case 5. A.W., 15 years. Bilateral Acute Frontal Sinusitis with Osteomyelitis and Cerebral Abscess.

History of a "cold", followed by severe left frontal headache of increasing intensity over two weeks, with swollen painful left eyelid during the second week of that period. Treated with sulphonamides, with little improvement.

Examination. Some puffy swelling all over the frontal area, but no real oedema: tenderness chiefly on left side.

Treatment by inhalations, etc., and full dosage of sulfadiazine, in spite of which temperature continued to rise and pulse rate fell to 55-60/min. on third day: general condition not so good. Marked swelling, oedema and tenderness over frontal area. Some neck rigidity.

Treatment by Drainage Operation under general

anaesthetic. Limited drainage opening made in floor of each frontal sinus, revealing thick pus in right, mucopus on left, and rubber tube inserted and stitched in position: sinuses washed out with saline and Penicillin injected - 2 c.c. (2,000 units) in each.

Intranasal antrostomy (double) and middle turbinotomy.

Lumbar C.S.F. under pressure and cells increased.

Penicillin - I.M. Drip 100,000 units per 24 hrs.;
 locally 10,000 " " "
 (as 2,000 in each 4-hourly).

Swab of pus revealed Staph. aureus +++.

Day 2. Neck rigidity and Kernig's sign weakly positive: frontal headache.

Day 3. Sinus washings contained Staph. aureus.

Day 6. " " " no organisms on culture.

Day 10. Sinus tubes out and wounds stitched after 190,000 units (last sinus washing was later reported - left clear, right very few Staph. aureus).

Penicillin drip stopped after 900,000 units.

Headache: fundi oculi showed slight papilloedema.

Day 17. Papilloedema still present, and haemorrhage of right disc. Some swelling and tenderness over frontal area.

Treatment: operative removal of outer table of osteomyelitic frontal bone to a distance of 2" above orbital margin. Careful probing revealed Right Frontal Lobe Abscess containing 40 cc. of thick pus, culture of which yielded Staph. aureus.

Penicillin, 20,000 units in 2 cc. injected after wash-out: drainage tube clipped for 24 hours.

Injection repeated daily for six days.

Penicillin injected as above, tube clipped for 8 hours, and allowed to drain for 16 hours.

Abscess cavity has now closed down.

Case Summary:

Case of Bilateral Acute Frontal Sinusitis with Osteomyelitis of Frontal Bone and Right Frontal Lobe Abscess due to Staph. aureus treated by intranasal and limited extranasal drainage and Penicillin, under which apparent recovery was recorded on sixth day. Frontal sinus washing, however, showed reinfection and further investigation revealed Osteomyelitis and Cerebral Abscess, necessitating more radical exposure of frontal bone and drainage of abscess.

Case 6. Mrs M., Chronic Maxillary Sinusitis
(Dental).

History of dental extraction ten years ago followed by infection of left antrum which has required repeated wash-outs ever since. Complains of headache and post-nasal discharge.

Examination: Septal deviation to the left: small fistula from mouth to antrum through 2nd molar tooth socket.

X-ray revealed mucous membrane thickening of
left antrum: other sinuses clear.

Treatment: Antrum washed out by cannula through fistula, yielding pus.

Specimen on culture yielded scanty Strep. viridans
and Diplo. catarrhalis.

Days 1-4. Penicillin, 20,000 units in 2 cc. instilled into left antrum daily for four successive days. Penicillin did not leak back through the narrow fistula.

Days 5-6. No treatment.

Day 7. Antral wash-out yielded thick yellow material culture of which gave the same result as above.

Patient instructed to wash out antrum daily.

Case Summary: Case of chronic maxillary sinusitis treated by lavage and Penicillin instillation for four successive days, with no improvement.

CONCLUSIONS.

The small series of cases recorded is too limited to allow of any definite conclusions being drawn: the principles elucidated can, however, be taken as confirming impressions already formed, and will add to the accumulating mass of evidence of the value of Penicillin in certain classes of infection.

One or two of these cases are highly instructive as regards future management of acute fulminating sinusitis.

Case 1 demonstrates the inevitably fatal termination of a late case (? 3 weeks) even in the days of sulphonamide and surgery, while Case 2 shows that given early enough treatment, recovery can be expected with sulphonamides and intranasal drainage.

According to previous statistics, Case 3, with commencing osteomyelitis of frontal bone progressing in spite of limited surgical drainage and sulphonamides, would almost certainly have ended fatally. Penicillin produced dramatic cure within five days. Of a very similar nature but treated by limited drainage and Penicillin from the start, Case 4 resulted also in recovery but less rapid, perhaps due to the unusual causal organisms.

Case 5 demonstrates very well the controlling

power of Penicillin over the acute infection, but at the same time makes it very obvious that Penicillin therapy will never replace adequate surgical drainage and removal of necrotic bone.

Thus it can be seen that the ideal treatment consists of complete control of the original acute infective stage, now possible with the use of Penicillin, and later any necessary treatment of residual infection or sequestra. In some cases this later treatment will not be required and healing will take place without radical surgical procedure (Putney, 1944). In any case the supreme advantage lies in the fact that no longer are extensive operations required at a critical period of the illness.

With regard to chronic infections of the sinuses, I have recorded only one case, but even that supports the results with other medications and the findings of other workers with Penicillin (Putney, 1944) that until the chronically thickened, infected and granulating mucous lining is removed surgically, no local antibacterial therapy will be of any avail.

TABLE OF CASES.TABLE XXI.

| Case | Complication | Organism | Treatment | Result |
|------|--|---|---|---|
| 1 | Meningitis | Staph. aureus | Drainage and (Sulphapyridine <u>Sulfadiazine</u> | Death |
| 2 | Oedema of Orbit | Staph. aureus | Drainage and Sulfadiazine | Recovery |
| 3 | (Orbital Abscess (?Osteomyelitis | Staph. aureus | (Drainage and ((Sulfadiazine ((Penicillin (Radical | Recovery in 5 days |
| 4 | (Orbital Abscess (Osteomyelitis | (Anaerobic (Streptococci (Leptothrix | Drainage and Penicillin | Recovery in 11 days Recurrence |
| 5 | (Osteomyelitis (Frontal Lobe Abscess | Staph. aureus | (Drainage and (Penicillin (Radical expos- ure | Apparent recovery Complication and recovery |
| 6 | Chronic Infec- tion | Strep. viridans | Local injections of Penicillin | No change |

S U M M A R Y.

The agent, Penicillin, is discussed with a view to possible local application in the nose and throat, suitable vehicles chosen, and administration decided.

Bacteriological and clinical methods are detailed.

A series of experiments prove that the Penicillin lozenge will sterilize the surface of the fauces within eight hours, and that this means can be used for pre-operative preparation and post-operative control in tonsillectomy. It will not sterilize the tonsillar crypts even after prolonged administration.

The normal process of healing after tonsillectomy is described, and a scheme for the investigation of possible improvement by the use of Penicillin is put to trial. Results show that the improvement is greatest in the immediate post-operative phase, best results being obtained with administration of lozenges every two hours for sixteen hours before and eight days after tonsillectomy. A series of 77 cases is detailed.

The aetiology of Vincent's infection is reviewed, and the various forms of treatment discussed. A new method of therapy is suggested, using only Penicillin lozenges every two hours for 4-5 days followed by

eradication of predisposing factors. Details of ten cases illustrate the efficacy of this method.

Various treatments of acute tonsillitis are discussed and the place of local Penicillin therapy defined, by conclusions derived from eight cases treated, as effective prophylaxis and treatment of early cases, but only as an adjunct to general treatment in later cases.

The use of local Penicillin in Peritonsillar abscess permits safe tonsillectomy very soon after incision: in streptococcal carriers renders them clear during use of the lozenge: in streptococcal gingivitis is the treatment of choice.

Local nasal administration of Penicillin is best by means of a snuff inhaled from specially designed applicators, given every 2 hours over at most four days: it is effective bacteriologically and clinically in eliminating susceptible pathogens from the nose and so in preventing or curing the secondary infective stage of the common cold, although aids to decongestion may also be required: 38 cases are cited.

Sinus infection and its treatment is reviewed, and modern treatment with local and general Penicillin described. Six cases are described in detail with the conclusion that in the acute suppurative form the

ideal treatment is conservative control of the critical and dangerous early stage, by Penicillin and minimal surgical drainage, leaving any further interference till a later and safer date: in the chronic condition local Penicillin therapy has no advantage over surgery.

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